IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

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SHIRE DEVELOPMENT INC., SHIRE PHARMACEUTICAL DEVELOPMENT, INC., COSMO TECHNOLOGIES LIMITED, and GIULIANI INTERNATIONAL LIMITED,	:	CIVIL ACTION
Plaintiffs,	:	
v	:	
CADILA HEALTHCARE LIMITED (d/b/a ZYDUS CADIL) and ZYDUS PHARMACEUTICALS (USA) INC.,	:	
Defendants.	:	NO. 10-581-KAJ

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Wilmington, Delaware
Monday, March 28, 2016
Bench Trial - Volume A

- - -

BEFORE: HONORABLE **KENT A. JORDAN**, U.S.C.C.J.

APPEARANCES:

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P R O C E E D I N G S

(REPORTER'S NOTE: The following bench trial proceedings were held in open court, beginning at 9:02 a.m.)

THE COURT: Good morning. Please be seated.

(The attorneys respond, "Good morning, Your Honor.")

THE COURT: This is the time set for trial in this matter, Shire versus Cadila Healthcare. And we have no jury in the box, a bench trial, so we can dispense with some formalities. Why don't we go ahead, though, and start with introductions. Shire.

MS. FARNAN: Good morning, Your Honor. Kelly Farnan from Richards Layton & Finger on behalf of Shire. I have with me my co-counsel from Frommer Lawrence & Haug. Ed Haug.

MR. HAUG: Good morning, Your Honor.

THE COURT: Good morning.

MS. FARNAN: Jason Lief.

MR. LIEF: Good morning.

THE COURT: Good morning.

MS. FARNAN: Angus Chen.

MR. CHEN: Good morning, Your Honor.

MS. FARNAN: And Liz Murphy.

MS. MURPHY: Good morning, Your Honor.

MS. FARNAN: And also Jason Rawnsley, you might see him throughout the week.

MR. RAWNSLEY: Good morning, Your Honor.

THE COURT: Good morning.

MS. FARNAN: And I think Mr. Haug will handle the opening and may introduce some other folks.

THE COURT: And your presence indicates that the issue we discussed at the pretrial conference has been resolved to the satisfaction of everyone; am I right?

MR. PHILLIPS: It has, Your Honor.

THE COURT: All right. Thank you, Mr. Philips. Thank you, Ms. Farnan.

MS. FARNAN: Thank you, Your Honor.

MR. PHILLIPS: Your Honor, Jack Phillips on behalf of the defendants. With me in the court is Mike Gaertner.

MR. GAERTNER: Good morning, Your Honor.

MR. PHILLIPS: James Peterka.

MR. PETERKA: Good morning, Your Honor.

MR. PHILLIPS: Andy Miller.

MR. MILLER: Good morning, Your Honor.

And Andrea Wayda from Locke Lord.

MS. WAYDA: Good morning, Your Honor.

THE COURT: All right. Good morning.

Thank you, Mr. Phillips.

All right. Without further ado, why don't we begin with openings.

MR. GAERTNER: Your Honor, may I address an issue, just one housekeeping matter that deals with the

order of witnesses?

THE COURT: All right, Mr. Gaertner.

MR. GAERTNER: Your Honor, this issue came up briefly during the pretrial conference, and I want to make sure we have your guidance on it because we had a little bit of dispute with Shire leading up to the trial.

There are a number of what we would call testing declarants, that is, some labs and individuals that did testing, didn't render any opinions. They did the test, passed the test off to an expert who is going to render an opinion on this.

We thought that we were keeping open the option not to call those as live witnesses, the declarants, because of the time constraints and, in fact, included on our exhibit list their declarations so our testifying experts could rely on those declarations when they testify. And we ran -- got a little bit crosswise with the plaintiffs as we headed off to the trial date, and it seems to me, and maybe Mr. Haug can clarify for me, but it seems to me they're going to object to our experts relying on the declarations because the declarants are not present to sponsor those declarations even though there is no objections to them.

I just want to make sure that in your view, Your Honor, if there is no objection to the declaration, our experts can rely on the testing declarants' work.

THE COURT: I will hear from Mr. Haug.

MR. HAUG: Thank you, Your Honor. The issue really is we did not reach agreement on not having experts testify about their testing. The reason it came up at all, the thought was maybe that was a way to save time, but it's not a lot of time in opening in these, but we didn't reach agreement. And so if they want to put in testing evidence, and put it in the record, I think they have to have an appropriate sponsoring witness.

THE COURT: Yes.

MR. HAUG: That's all.

THE COURT: Okay. Well, Mr. Gaertner, I'll give you the last word.

MR. GAERTNER: They didn't object to the declarations that are on the exhibit list.

THE COURT: Well, I'll not sure why you think their failure to object to the declarations means they're waiving their objection under the Federal Rules of Evidence. They may say, fine, put the declaration in, but I am not certain that that means we have agreed to stipulate that the declaration will substitute for the witness. You either agree or you don't agree, right? And if you don't agree, then we're bound by the Rules of Evidence. I can't -- yes, that's where I stand.

MR. GAERTNER: And that's fine. We're prepared

to present them. We just wanted to make sure we did the right thing. Thank you, Your Honor.

THE COURT: Okay. Mr. Haug.

MR. HAUG: May it please the Court, this is a one patent case, Your Honor. And I'd like to, just very briefly, the first slide is just Shire. Shire is a biopharmaceutical company that is in a lot of different areas and, in particular -- if we can have the next slide, Kyle.

They market a product called Lialda. Lialda was approved in 2007 with a NDA. Lialda, the active ingredient in Lialda is mesalamine. It is a delayed release tablet which is currently indicated for the induction of remission in adults with active, mild, to moderate ulcerative colitis, a very difficult disease, and for the maintenance of remission of ulcerative colitis.

So that is what it has been approved for. It's been on the market since 2007.

In 2015, I believe the sales just went over $1 billion.

THE COURT: Hold on one second, Mr. Haug.

First, with the demonstratives like this, is everyone comfortable with having me have a copy of those?

MR. HAUG: Actually, I am not comfortable having forgotten to give them to you.

THE COURT: Okay.

MR. HAUG: If I may approach, Your Honor.

THE COURT: Yes, you certainly may.

And just so we're clear, I think people understand this.

(Binders passed forward.)

THE COURT: Thanks very much.

We are timed. Everyone knows that. When you are on your feet, the clock is running against you. If there is an objection, and we have to absorb a lot of time, I'll figure out how to split that time or charge it all to one side or the other. All right? I will try to be fair to everybody on that.

Okay. Go ahead.

MR. HAUG: Next slide, Kyle.

So the defendants in this case, Zydus, one of them is Cadila Healthcare, Limited, which is based in Ahmedabad, if I pronounced that correctly, which is India, and they have a U.S. subsidiary, Zydus Pharmaceuticals, USA, and that subsidiary is the one that filed the ANDA in this case.

Go to the next slide.

Cadila Pharmaceuticals, or I should say Cadila Healthcare, Limited is the manufacturer of the product and what we see here in slide PDX-1.4 is the label, the label

that is in their ANDA, showing that it is manufactured by Cadila Healthcare, Limited in Moraiya, spelled M-o-r-a-i-y-a, which is in India. They filed this ANDA in 2009.

If I can have the next slide, Kyle, please. Thank you.

I am not going to go through all these things on this slide, but this is just the timeline for the case. And if we go all the way to the left, so that is the original ANDA submission was in December of 2009.

And if we go along on the bottom of the timeline, go all the way to October 22, 2013, about four years later, that is when Zydus filed a resubmission, if you will, of its ANDA with the FDA, and then this case was reopened thereafter, and here we are.

To this point in time, there has not been an approval to my knowledge.

The patent, one patent case, as Your Honor is very well aware, it's the '720 patent, as we have referred to it, filed in June of 1999.

At a very high level, this invention, the invention is really about how you control release of mesalamine, that is the active ingredient. Mesalamine has been around a very long time, but it is a very soluble, very fast releasing drug. If you just took mesalazine and

ingested it, it would go in your system. The disease we're trying to treat, ulcerative colitis, is mainly in the large intestine. So the goal here is to get the active ingredient so that it can be locally acting in the large colon. So it takes hours to get there.

So the challenge is how do you control the release of mesalamine so it doesn't release long before it gets to the point in the body where it does what it is supposed to do.

In addition to that challenge, the inventors also were faced with the dosage form itself. You need a lot of active, 1,200 milligrams, and the claims, we'll see the claims in a second, they require at least 80 percent of the total weight of the tablet is mesalamine. That is an unusual percent active.

So the challenges are how do you get a tablet with a lot of active ingredient in it and how do you control that release?

And the invention they came up with is a two matrix system. More about that in a bit.

Can we have the next slide, please.

THE COURT: I don't want to be --

MR. HAUG: Certainly.

THE COURT: I am just curious because we have the court reporter taking this all down. What is the name

of the active ingredient here. Mesalamine?

MR. HAUG: Mesalamine, which is synonymous with mesalazine. It's the same thing. It is just spelled differently and it has a chemical name, too. But it's the same thing.

So the title of this patent, mesalazine is mesalamine. We will I think largely always be referring to it as mesalamine, with an M.

THE COURT: Okay.

MR. HAUG: That is the same thing.

THE COURT: Okay.

MR. HAUG: This slide, 17.7, is the claim construction from the Court. The claim construction that -- well, I should say the claim terms, and I am going to go through those in a second.

But "inner lipophilic matrix,"

"Outer hydrophilic matrix,"

"Melting points," and also,

"Wherein the active ingredient is dispersed both in the lipophilic matrix and the hydrophilic matrix" I think are the main terms.

There is also I think a dispute about "consisting of" and the extent of that language and its impact on the infringement proofs here.

Next slide, please.

The parties did agree to a few claim terms before the claim construction.

That was "matrix," "a macroscopically homogenous structure in all its volume."

And then the two words which you will hear a lot in this case, "lipophilic," which was agreed to mean "a poor affinity towards aqueous fluids," not no affinity but poor affinity.

And "hydrophilic" was agreed to mean "has an affinity for water."

So the claim, we have one claim, one independent claim, claim 1.

Claim 1 I have highlighted in yellow here some of the undisputed facts, right?

"Oral pharmaceutical compositions," as I have indicated here, that is not a dispute in this case.

Zydus has an oral pharmaceutical composition.

Similarly, Zydus has an active ingredient which is 5-amino-salicylic acid. That's the chemical name for mesalamine. They have that. There is no dispute, obviously.

And then if we go all the way down to the lower element C in the claim, "wherein the active ingredient is present in an amount of 80 to 95 percent by weight of the total composition," that also is not in dispute because that is what the Zydus formulation contains.

So what are the disputes? The disputes I've indicated here in red, one, claim element 1A, inner lipophilic matrix. Does Zydus have an inner lipophilic matrix consistent with the claim construction in this case?

Another point in dispute is the melting point. Is the inner lipophilic matrix, or I should say the excipient, which is in the inner lipophilic matrix or is the inner lipophilic matrix, which in this case is magnesium stearate, does magnesium stearate have a melting point below 90? That is a disputed fact and, clearly, an issue in the case.

While I'm looking at that right now, I should also point out, Your Honor, that the claim here is literal infringement of claim 1. However, with respect to this claim element, should the Court find there is no literal infringement, there also is an assertion of infringement under the doctrine of equivalents.

The doctrine of equivalents allegation is that is the magnesium stearate that Zydus uses is equivalent in function, way and result to another ingredient, which in this case we say would be stearic acid, which clearly falls within the scope of the 1A group consisting of, and stearic acid is also used in the patent examples.

And so the claim that we're making is that if we

need to get to the doctrine of equivalents that the magnesium stearate, should the Court find that the melting point is above 90, it operates in the same way, functions the same way to ultimately give the same result. So that's the doctrine of equivalents case that is also going to be presented.

Then we have another disputed claim element, which is 1B, the outer hydrophilic matrix, and much like the dispute with 1A, the question simply is -- not simply, but the question is, does Zydus' formulation have an outer hydrophilic matrix as called for in claim 1B? And in this case, we believe the outer hydrophilic matrix consists of two excipients. One is sodium starch glycolate, SSG, and the other is sodium carboxy methyl cellulose, which is CMC. And so we'll be using those, I think, abbreviations, if you will, CMC and SSG. That's what they mean.

But, in any event, we assert, we believe the evidence will show that the outer hydrophilic matrix in the Zydus product consists of those two excipients at least, and at the inner lipophilic matrix consists of magnesium stearate.

THE COURT: Give me those two excipients again with SSG --

MR. HAUG: SSG, sodium starch glycolate, and the other is sodium carboxy methyl cellulose, CMC.

So we believe we will establish infringement here of the Zydus product by a preponderance of the evidence in a number of ways.

First, by looking at the Zydus manufacturing process itself, how do they actually make their formulation? And we believe the evidence will show that by looking at their formulation manufacturing process that is set forth in their ANDA together with the experts who analyze it and opine on it, we believe that will be very compelling evidence that the matrices are being formed as covered by this patent.

In addition to that, we have internal development documents from Zydus as well as some analyses that Zydus itself made about their product during the development that we also think are relevant to the issue of infringement.

And we have Zydus testimony. Now, the Zydus testimony, there is -- Your Honor will hear one of the witnesses by deposition. He's the head of pharmaceutical development, if you will, from Zydus. He's resident in India. He was deposed. We believe he was a 30(b)(6) witness. I think there may be an issue that we'll have to address if Zydus raises it, but we believe it was a 30(b)(6) deposition taken of Mr. Kulkarni, and he made a number of admissions on behalf of Zydus that we believe as a factual

matter are highly relevant to the question of infringement.

And then, lastly, we have Shire expert testing and analysis, which I'm going to very briefly touch on.

Now, back to Zydus development.

Kyle, if I could have PTX-299.8. Can we blow that up? A little more.

This is an exhibit which is not objected to, PTX-299.8. This is a slide that was sent by the head of development for Zydus to an in-house patent attorney, or at least someone they believe was a patent attorney. And Your Honor may remember, we had quite an issue about privilege on some documents. This is one of the documents that was deemed not to be privileged.

So as it says, formulation strategy to circumvent OB, that means Orange Book Patent No. U.S. 6,773,720. And they have three ways, if you will, to circumvent, as the title of this slide says, the patent. And this will be discussed a bit by Mr. Kulkarni in his deposition, and the first point is the active ingredient should be present in an amount of 70 to 75 percent by weight of total composition.

Your Honor may recall, I just had claim 1 up there, and the claim limitation says it has to have at least 80 percent. So this was considered to be a way around the 80 percent limitation. In the end, Zydus' formulation has

over 80 percent. So they did not pursue that.

Number two, the inner matrix is hydrophobic in nature instead of being lipophilic.

Now, hydrophobic means repels water, and the testimony is going to show that the Zydus people believed that if they had something which was hydrophobic, that would not be lipophilic. As it turns out, as a scientific matter, magnesium stearate, which is what they used, is lipophilic. They believed it was hydrophobic, but for purposes of this patent and the claim construction we have with this patent, if you have something which is hydrophobic, it's still lipophilic. And so they went with option two.

And, number three, they have the release of core tablet is controlled by polymer coating instead of by matrix formulation. So, in other words, the thought there being they would have a core of active material and they would coat it with a polymer. That was a different way to formulate this product as opposed to using a matrix formulation. In the event, Zydus went with a matrix formulation.

So the next slide, 1.13. So here are some of the we believe to be admissions. Certainly, it's the testimony of Mr. Kulkarni in his 30(b)(6) deposition. For example, magnesium stearate is hydrophobic.
Roll-compaction, that was part of the Zydus process of

manufacture, is a dry granulation method. Zydus' dry granulation stage creates granules.

The granules from Zydus' dry granulation stage contain mesalamine, the active magnesium stearate, which we believe is the lipophilic excipient, and colloidal silicon dioxide and other excipients.

It goes on. There are no hydrophilic excipients in Zydus' dry granulation manufacturing.

Carboxy methylcellulose is hydrophilic. Carboxy methylcellulose is the sodium carboxy methylcellulose I was just referring to.

And then right below that, sodium starch glycolate is hydrophilic. That's the second of the hydrophilic excipients I was referring to in the outer hydrophilic matrix.

And then lastly, Zydus' product exhibits swelling upon contact with aqueous fluids, and this swelling is attributable to its hydrophilic excipients. So I point this out because these are statements made by Mr. Kulkarni, which will be presented to the Court later today.

So the last piece of evidence or the last tranche of evidence, if you will, that we believe shows infringement -- if I could have the next slide, Kyle, thank you. Next one. I'm on 1.11, 1.11. There we go.

Testing by Shire's experts. Your Honor is going

to hear from a number of experts. While the number may be large of experts, many of them will be short. And so we intend to be as focused and crisp as we possibly can be, and a number of these are testing people.

The first one, Vivian Gray, will talk about dissolution testing and imaging of the Zydus product.

Dr. Hoag is going to talk about what's called the drop penetration test, which simply shows the penetration of water into different formulations to show whether the inner lipophilic matrix, whether water penetrates at the same rate as in the outer.

And then we have Dr. Hanton, who has a series of tests that were conducted largely going to determine the melting point and also the, whether or not the magnesium stearate used by Zydus is what we call in a hydrated state or an anhydrous state. More of that during the trial.

And then, lastly, Dr. Davies, he conducted Raman spectroscopy and also did some optical microscopy. Dr. Davies is the expert that trial testimony will be presented by deposition, and I thank the Court again for allowing us to present his testimony in that way.

So those are the tests that have been conducted by Shire's experts and that will be introduced into this case.

1.15. This is just an optical microscope from

Dr. Davies, which Your Honor will see. And what you see in that circle, if you will -- it's not really a circle -- that's supposed to be a G. The testimony is that that is a G. All Dr. Davies was doing, he was asked to pick out a granule in this optical microscope of the cross-section of Zydus' tablet, so that's what he did. So there's a granule.

And then the next slide, 1.16, this is a Raman map, as it's called, which shows the presence of mesalamine. The different coloring, whether it's yellow, orange, red, that goes to the intensity of the amount of mesalamine that is present in the different cross-sectional areas, and the testimony will further explain that.

Now, if I can go to 1.14. I already mentioned the one part of this case is doctrine of equivalents. Again, essentially, what we're asserting is that this is claim element 1A, and it's an inner lipophilic matrix consisting of, and what's highlighted is, hydrogenated fatty acid, salts.

Magnesium stearate is a hydrogenated fatty acid, salt. It's a salt. Okay. Again, if Your Honor finds that the melting point is not below 90, which we assert that it is, but if Your Honor finds that it's not, stearic acid is also a hydrogenated fatty acid. Magnesium stearate, as I said, is the salt of stearic acid. It's very close, very

chemically similar. And magnesium stearate and stearic acid are both lipophilic. And stearic acid has a melting point well below 90. So that is the essence of our doctrine of equivalents case.

Just a very short couple of words, if you will, on the validity Zydus of the case.

All I've shown here is to my understanding, Zydus is claiming that the patent is invalid for one of two reasons, or maybe two reasons.

One is they assert invalidity under 103, obviousness. Under reference, which is U.S. Patent No. 5, 593,690, called Akiyama, A-k-i-y-a-m-a. That Akiyama reference was considered during the prosecution of this patent. It is not directed to mesalamine, but, in any event, they point to this reference as a primary reference to my understanding showing that the '720 patent is obvious in combination with one or more of the 17 other references.

Now, these 17 references are what are contained in the pretrial order in this case. I doubt they will go with 17 references, but I will let Mr. Gaertner speak to that.

And then the other ground of invalidity is under 112, asserting that the patent does not satisfy the requirements of 35 U.S.C. 112.

And with that, Your Honor, I would just close this opening, saying that we intend to offer five live witnesses today. And time permitting, two witnesses, maybe three by deposition.

THE COURT: All right.

MR. HAUG: Thank you.

THE COURT: Thank you, Mr. Haug.

Mr. Gaertner, your opening.

MR. GAERTNER: Good morning, Your Honor. Mike Gaertner. And may I approach?

THE COURT: Yes. Please.

(Binders passed forward.)

MR. GAERTNER: The '720 patent has a very specific composition that has a very specific limitation: "excipient structure of properties and dispersion of the active ingredient."

Can we go to slide 3, please.

On slide 3, Mr. Haug has taken to the evidence that he thinks he is going to show in this case. And on behalf of the defendants, I'd like to walk you through the issues we think are critical and what we believe the evidence will show.

Now, the plaintiffs have the burden of proving that:

The Zydus ANDA product has an inner lipophilic

matrix that has the required excipients. They're very narrowly defined.

A required structure, which we really didn't hear a lot of discussion about in the opening for plaintiffs. And,

Exhibiting the required properties.

Now, the plaintiffs also have the burden of showing that the Zydus ANDA product has mesalamine in the inner matrix and the outer matrix.

We believe the evidence will show that the plaintiffs will be unable to meet their burden on any of the elements and any one of these will be dispositive in this case.

At the end of this as well, Judge, we'll talk a little bit about the invalidity case as well.

Could you go to the next slide, please.

Now, the required excipients really break down to two aspects. Mr. Haug has mentioned one of them, and that is "melting point." That is an issue in dispute.

Mr. Haug pointed out some of the experts that the plaintiffs will be presenting. The defendants will be presenting several experts themselves. Dr. Thomas O'Halloran from Northwestern University did an open capillary melting point test that is required by the USP. He will present the evidence on that.

We will be presenting Professor Mark Sacchetti from the University of Wisconsin. He performed two tests: a DSC test and a hot stage microscopy. And, actually, that is a still image from the hot stage. That will be a movie test. It is a melting point test where it films the temperature as the crystals enter the microscope, and we believe that evidence will be very compelling ultimately of the outcome of the melting point limitation.

THE COURT: What does DSC stand for?

MR. GAERTNER: Differential scanning calorimetry.

Add the defendants will be presenting Dr. Hollingsworth from Kansas state who is an expert in solid state chemistry to opine on the melting point as well.

That is one aspect of the required excipients that the plaintiffs would have to show is in the inner lipophilic matrix.

Now, the second aspect of the required excipients -- and we can go to the second point, the next slide, excuse me -- is the "consisting of" limitation.

And I think Mr. Haug touched on it in his opening statement but didn't discuss it that much. And this is where I would like to talk a little bit about how this product comes together.

And you heard Mr. Haug talk about magnesium

stearate. And magnesium stearate is the alleged lipophilic forming agent in this case. Magnesium stearate is a lubricant.

THE COURT: Let me stop you for a second. You said it is the "alleged."

MR. GAERTNER: I am sorry.

THE COURT: You said it is the "alleged."

MR. GAERTNER: Yes.

THE COURT: It is the alleged lipophilic matrix, is that what you said?

MR. GAERTNER: The lipophilic forming matrix, yes. You heard Mr. Haug talk a lot about magnesium stearate in his opening. He says the lipophilic matrix is formed by the magnesium stearate.

I want to get to the slide Mr. Haug talked about, but also I'd like to talk about just generally what is going on with the product, not to go into detail but to put some context on it. And that is, for lack of a scientific word, mesalamine, the active ingredient, it is sort of fluffy, and to make it work in the Zydus formulation, Zydus decided to roll or compact the mesalamine. Now, roll or compaction, sort of as the name suggests, is rollers. You pour the active ingredient in and the roller compacts, smushes, it compacts the active ingredient.

Well, you are going to hear testimony from

another Cadila formulator, a gentlemen named Kieran Hoffer. It will be by deposition, and he was the formulator who decided to put the magnesium stearate in the roller compaction. And he is going to testify he did it because the magnesium -- I am sorry -- the mesalamine was sticking to the roller compaction as it was going through. So he added lubricant to make sure it came through smoothly.

THE COURT: So the reason you say this is the alleged excipient is because the position that Zydus was taking here is that magnesium stearate is not an excipient in the drug. It was a lubricant for the machinery.

MR. GAERTNER: Yes. It is a lubricant and does not form a matrix. That's right, Your Honor.

THE COURT: Okay.

MR. GAERTNER: You know, Mr. Haug put up a slide, I think it was slide 15. In all events, he talked about the various options, you might recall that, that one of Zydus formulators was looking at a time. And I think he said he went with option 2 which is hydrophobic matrix.

The evidence is going to show that that is a very early stage development document and that that, none of those, that option was not pursued. A different option was pursued to actually avoid putting those sorts of elements into the inner volume of the Zydus product.

But I bring that us up as an aside because

really my point is a little bit different. That is, in this roller compaction, I just mentioned you have magnesium stearate that it helps with the lubrication. Mesalamine comes through.

On the slide is the bill of materials which is the actual ingredients that go in that step. The second element there, colloidal silicon dioxide, that is hydrophilic. So to the extent the plaintiffs are going to endeavor to prove that those granules, which is a word that Mr. Haug mentioned in his opening, if that is their theory, that they're going to prove that granules form a matrix, well, there is colloidal silicon dioxide which is a hydrophilic component which is in these matrixes, too.

What does that do? Consisting of, it is limited only to the Markush group limitation. That means that it excludes only substances un related to the claims or impurities, and we will show the evidence that it is neither unrelated nor impure.

Let's go to the next slide.

I'd like to talk next about the other requirement of the '720 patent. We haven't had a discussion of that, and that is the structure.

There must be a matrix, and the claim limitation matrix, and this is agreed construction as Mr. Haug pointed out, it means "a macroscopically homogenous structure in all

its volume."

Now, they used the images from the prosecution history for what the patent, they submitted to the Patent Office to describe a matrix structure. And what we're going to see as the evidence proceeds is that the plaintiffs will not be able to show a matrix structure in the Zydus ANDA product, consisting of magnesium stearate.

If we could go to the next slide.

THE COURT: Will they be able to show a matrix structure consisting of any other chemical compound? You just said they wouldn't show it, a matrix --

MR. GAERTNER: That takes me back --

THE COURT: -- structure.

MR. GAERTNER: -- to the preceding point. Judge, if their theory is that the granules come out of the compaction step, and that is the matrix or some part of that is the matrix. If that is the matrix, and I am not sure what the structure of that is, when we get to that in a second, because there is another element of the structure that is important to your question. But if that is matrix, that is why I brought you back to the colloidal silicon dioxide because there will be a hydrophilic component in that as well.

But to further answer your question, I think the next slide is helpful. If you could go to slide 6.

Two aspects to the structure. One is matrix. The other is -- I am sorry, I think it's slide 7. I think I misspoke. Slide 7. Thank you.

And the other aspect is dispersed.

This is plaintiffs' claim construction. They have, plaintiffs advocated this claim in the structure and the Court awarded to it.

So the construction of "dispersed" is "sufficiently mixed to incorporate one substance into another."

And so, Judge, if you put those two terms together, "matrix" and "dispersed," at the end of the day, we believe that plaintiffs are required to prove that the mesalamine is sufficiently mixed to incorporate it into a macroscopically homogenous structure in all of its volume and consisting of magnesium stearate.

That is what the plaintiffs will have to prove here, and we believe they will be unable to meet that burden.

If we can go to the next slide, please.

The next slide implicates the properties of the matrix. And we've had a lot of discussion about that in the prior claim construction hearing. And one of the things that struck me when Mr. Haug was up here is he talked a lot about the excipient that was in the alleged matrix but not the properties of the matrix. And remember, Judge, that is

actually what the Federal Circuit shot down in the Shire V Watson case. That is, the matrix is defined by the presence of excipients. The entire matrix has to have a certain character.

Now, there was some testing done, and Mr. Haug touched on that testing. Two I think tests are particularly important here that you will have to take a look at:

One is the so-called drop penetration test that Dr. Hoag did in an effort to show lipophilicity. That wasn't done on the Zydus ANDA product, that was done on some other powder compacts that Dr. Hoag created in his laboratory.

I mean the Federal Circuit has been clear that to prove infringement, you need to do testing on the ANDA product. That testing was not done.

The second aspect of the testing I think you are going to hear about was some dissolution testing that was done by Vivian Gray and reviewed by Dr. Little. Dr. Little is going to circle some images on that and do various things, and you will hear what his testimony is. But I do think the testimony will not be, that the plaintiffs can show that there is any particular element in what they claim to be the alleged matrix.

Let's go to the next slide, please.

And the final limitation I am going to talk

about this morning before we move on is "dispersed in both." We talked about what "dispersed" means, "sufficiently mixed to incorporate one and another."

Plaintiffs will also have to show that mesalamine is incorporated both in the inner lipophilic matrix as well as dispersed in the outer hydrophilic matrix.

Zydus only adds mesalamine in one step of its manufacturing process. It doesn't add it in two. And we believe the evidence will show that there is no second addition and no separate dispersion, excuse me, of the mesalamine in the alleged outer hydrophilic matrix as well.

Mr. Haug put on the screen a granule, I think it was of Dr. Davies. That, I have the number down. That is PDX-1.15. Dr. Davies did circle that page which he purports to say was a granule but you will hear his de bene esse deposition later either today or tomorrow and the testimony will be that Dr. Davies is not opining that is a matrix. Dr. Davis isn't opining he knows is in there. He will say he believes it is mesalamine in there, but he won't be able to say whether there is magnesium stearate, colloidal silicon dioxide, SSG, or the other various hydrophilic components that are in that alleged granule.

As a result of that, we believe the testimony, the expert testimony -- they're going to have a lot of it. There is no doubt they're going to have a lot of it. But we

believe that experts are going to ask you to see things that nobody else can see ultimately in an effort to try to cobble together that case.

Now, I'd like to touch briefly on Doctrine of Equivalents which is my next slide.

I will be quick because I'd like to wrap it up and get on to the evidence.

Magnesium stearate is a lubricant. It is not chemically similar to stearic acid which is a known matrix forming agent and it does not form a matrix. It does not do the same function in the same way and have the same result. We believe the evidence will be very clear on that, and that their Doctrine of Equivalents argument will not prevail.

Finally, on invalidity. Next slide.

One thing that was not touched on the opening that we think it is a powerful invalidity defense is our indefinite defense.

We believe the evidence will show that under the plaintiffs' theory, and we believe they're going to advance the theory that you can have both hydrophilic and lipophilic elements to a matrix. Under that theory, the patent is indefinite because it provides no parameter for a person of ordinary skill in the art to determine what is hydrophilic or lipophilic.

The second thing is the obviousness defense,

that is the one thing Mr. Haug talked about. I want to make a correction here. We're not claiming that we need 17 combinations to prove our obviousness defense. In fact, in the pretrial order, we say it is clear -- I forget the paragraph but it is in there and we're saying we're relying on four references.

There is a lot of references in there for the background of the knowledge of person of ordinary skill but, no, we're not relying on them. We're going to show there are four references. You put them together. If you put those four references together that the patented invention is obvious.

Thank you, Your Honor.

THE COURT: Okay. Thanks, Mr. Gaertner.

Mr. Haug, your first witness.

MR. HAUG: Shire will call Andrew J. Stautberg.

... ANDREW J. STAUTBERG, having been first duly sworn, was examined and testified as follows ...

THE COURT: You may be seated.

You may proceed.

MR. HAUG: Thank you.

DIRECT EXAMINATION

BY MR. HAUG:

Q. What is your occupation and title, Mr. Stautberg?

A. I am a Vice President at Shire Pharmaceuticals, and

my title is Product Strategy Team Leader.

Q. How long have you been with Shire?

A. I've been with Shire for just under six years.

Q. And prior to Shire, did you work somewhere else?

A. I worked for AstraZeneca for a little over 16 years.

Q. And how long have you worked in the pharmaceutical industry?

A. So adding those two together, I've been in the pharmaceutical industry about 22 years.

Q. And what are your responsibilities as Vice President and Product Strategy Team Leader for Shire?

A. I lead a team composed of representatives from different functions that have responsibility for the management of Lialda.

Some of those functions are, for example, clinical, regulatory, supply chain, as well as marketing and sales. And I also have direct responsibility for the U.S. marketing team.

Q. What are the responsibilities of the marketing team?

A. The marketing team has responsibility for defining marketing strategies, for defining the key messages that are to be used in advertising and promotion, for understanding the competitive environment that our product competes in. Those are some of the key responsibilities that they have.

Q. What does it mean to understand the competitive

environment for a product?

A. Some components of understanding the competitive environment would include understanding the product and understanding the products that our product, that Lialda competes with. So, for example, what the active ingredients are, what the indications are, the dose regimens, the strengths, the form, the pharmaceutical form.

Also, part of understanding the competitive environment would be understanding the disease, how it is treated, how it impacts patients as well as understanding how the product is performing and how it is performing versus expectations, how it is performing versus competition in terms of volume and sales, and market share.

Q. I'd like to ask you a few questions, background questions about Shire itself. What is the basic business of Shire?

A. Shire is a biopharmaceutical company. It is focused on rare diseases and certain specialty conditions with high unmet medical need. Shire invests in research and development to bring new treatments to market. It also end licenses technologies that were discovered outside of the company and works to develop treatments that can be brought to market to treat diseases that have high-end met needs. And then it also is involved in marketing and selling those products.

Q. And what are some of the therapeutic areas treated by the medicines that Shire brings to market?

A. Gastroenterology is one. Shire also has treated in hereditary angioedema, in lysosomal storage disorders, in endocrinology, and in neuroscience.

Q. Under what therapeutic area does Lialda fall?

A. In gastroenterology.

Q. What is Lialda?

A. Lialda is an oral tablet that contains 1.2 grams of mesalamine, or mesalamine, or 5-amino-salicylic acid, or 5-ASA.

Q. And what is Lialda's FDA approval for?

A. Lialda is indicated for the induction of remission in adults with active mild to moderate ulcerative colitis, and it is also indicated for the maintenance of remission of ulcerative colitis.

Q. Can you just briefly explain what ulcerative colitis is?

A. Sure. Ulcerative colitis is a form of inflammatory bowel disease. It is a disease that impacts the lining of the large intestine, so the colon and the rectum, and it's characterized by inflammation and ulceration of that colonic and rectal tissue.

THE COURT: Can I interrupt just a moment here?

THE WITNESS: Sure.

THE COURT: Just to note one procedural thing. The parties are clear on the sequestration responsibility and you've got that handled. Right?

MR. HAUG: I believe -- yes. I believe Mr. Stautberg is the only live fact witness.

THE COURT: Okay. Just making sure.

MR. HAUG: Thanks.

THE COURT: We're squared away. All right. Go ahead.

BY MR. HAUG:

Q. So you were -- what areas of the large intestine are affected by ulcerative colitis?

A. Ulcerative colitis always involves the rectum and involves the end of the colon, and depending on the patient, the disease can involve a larger extent of the colon extending in some patients all the way up the colon to the large intestine, or to the end of the small intestine.

Q. And what are the symptoms of ulcerative colitis based on your experience?

A. So I'm not a physician. I am offering my perspective as someone who has worked in the field for five years now on this particular product. But the cardinal symptoms of ulcerative colitis are rectal bleeding. That's from the ulcerations in the colon. Diarrhea, so the combination of the two is bloody diarrhea. Also frequency. So high

frequency of the need to have bowel movements. So sometimes patients need to use the restroom six to eight times per day as well as abdominal pain and cramping.

So this is, it's a pretty nasty disease, and when patients are having a flare of this disease, they are often not able to go to work. They are homebound. They need to be near bathroom facilities, et cetera.

Q. And what do you believe causes ulcerative colitis?

A. So it's not definitively known exactly what causes ulcerative colitis. It is an autoimmune disease, so it's in the same category as rheumatoid arthritis and psoriasis in that it is the body's immune system not working properly and the body attacking itself to cause this inflammation and ulcerations.

Q. All right. Are you aware of any cure for ulcerative colitis?

A. There is no medical therapy that can cure ulcerative colitis. Surgery is a cure. You can resect the diseased portions of the colon, but it's not a very good cure because it can leave patients with an ostomy, with an ostomy bag, and it can be -- impacts of surgery are so great that it's only used in the most severe cases.

Q. So how is ulcerative colitis treated in your cases?

A. In my experience, so mesalamines are the typical first line of treatment for mild to moderate cases of

ulcerative colitis, as well biologics for other immunosuppressive therapies are used for patients who don't respond to mesalamines, or who have more severe disease at their first presentation. And another common treatment for ulcerative colitis is steroids. Those are commonly used, but they are used short-term in order to get symptoms under control. They are not a good long-term option because of longer, of side effects of long-term use.

Q. And what is mesalamine?

A. Mesalamine is a -- it's the active ingredient in Lialda, and it is a locally acting drug that serves to reduce inflammation in the tissue that it comes into contact with.

Q. And based on your experience, how does mesalamine work to treat the symptoms of ulcerative colitis?

A. It works to treat the symptoms by reducing the inflammation in the diseased tissue that it comes into contact with, thereby allowing the body to heal itself. And by healing the ulcerations and reducing the inflammation, that takes care of the symptoms as well.

Q. How is mesalamine administered?

A. Mesalamine can be administered either orally or rectally.

Q. And what do you mean by oral or rectal administration?

A. So orally means ingested, so a tablet would be an example of an oral administration. Rectal administration would be in the form of a suppository or an enema, and that would involve administering the product to a patient and then having them lie prone for a period of hours so that the product -- so the mesalamine can come into contact with the diseased tissue, and it's not a very convenient option.

Q. How is Lialda administered?

A. Lialda is administered orally, so what that means is, it's administered orally. It needs to make its way through the, through the small intestine. It's coated in order to do so and not release while the product is in the small intestine. And once it reaches the large intestine, then the product delivers mesalamine throughout the, the large intestine.

Q. Do you know when Lialda was approved by the FDA?

A. Lialda was approved in 2007.

Q. And what was the indication at that time? Do you know?

A. The indication at launch in 2007 was for the induction of remission in adults with active mild to moderate ulcerative colitis.

Q. Was Lialda approved for any other indications?

A. It was approved in 2011 for the maintenance of remission of ulcerative colitis.

Q. At the time of Lialda's approval in 2007, were there any other oral mesalamine products on the market?

A. There were.

Q. And do you know what they were?

A. In 2007, the products on the market were Asacol and Pentasa, which were both mesalamine products, and Dipentum and Balsalazide, which we considered to be mesalamine products, but they are pro drugs of mesalamine, which means that the molecules in those products are converted in the large intestine into mesalamine.

Q. Does Lialda differ from any of those products in terms of its administration?

A. Lialda in 2007 was the first mesalamine product that was indicated for once daily dosing.

Q. And how many competitor products are there now in the oral dosage form, if you know?

A. So there are seven currently, eight if you consider a little longer period of time, and I will explain my answer. So Asacol, Pentasa, Dipentum and Colazal were the four that were available in 2007. Since that time, there has been a launch of four additional products. Asacol HD, Apriso, Giazo, and Delzicol. And in 2013, Asacol, which was one of the products that was available back in 2007, was -- was withdrawn from the market, or, more accurately, the manufacturer stopped manufacturing that product and making

it available.

Q. And who do you consider to be Lialda's primary market competitor today?

A. Our primary market competitors are Asacol HD, Delzicol and Apriso.

Q. And do you know what the dosing regimens are for those competitive products you just mentioned?

A. For Asacol HD and for Delzicol, those products are indicated to be dosed three times a day for the induction of remission. For Apriso, Apriso is indicated to be dosed once daily, but it only has an indication for the maintenance of remission of ulcerative colitis. It does not have an indication for acute treatment of ulcerative colitis.

Q. Do any of the competitive products have FDA approval for an indication for once a day administration?

A. Apriso would be the only one. And, again, that is only indicated for the maintenance of remission. So for patients who have already been put into remission on another therapy.

Q. Approximately how long had Asacol been on the market in 2007 when Lialda launched its product? Do you know?

A. Asacol was launched in 1992, so 2007, that would make it 15 years that Asacol had been on the market when Lialda was launched.

Q. And when Lialda came to market, who was the market

leader?
A. Asacol was.
Q. And what was their market share, if you know?
A. Asacol's market share at the time of the introduction of Lialda was about 60 percent.
Q. And how would you describe Lialda's performance since it launched in 2007?
A. Ever since Lialda has launched, it has had tremendous, tremendously successful performance. Lialda has grown to be the number two product in Shire. It has seen consistent growth in market share in volume and in sales.
Q. What is your basis for that testimony?
A. It's my job to manage the product and manage the expectations internally and to measure the performance or lead the team that measures the performance externally.
Q. And have you noticed any trends in the market regarding Lialda's performance or uptake?
A. So as I mentioned, it has grown consistently. One remarkable thing is that it has continued to grow consistently over a very, very long period of time, and an unusually long period of time in the pharmaceutical industry.

We're in our ninth year now since launch and the product continues to grow very rapidly. It is the number one most prescribed mesalamine, and I think in 2010,

I'm sorry, 2010 -- in 2015, it was still growing ten percent in terms of volume growth, and that is in a completely flat market. So the market is not growing at all and our product grew ten percent in the eighth year on the market.

Q. Based on your experience, has Lialda been profitable for Shire?

A. Lialda has been profitable since the year after launch and consistently so throughout its life.

Q. Do you know what Lialda's current market share is?

A. The market share from January of 2016 was 37.3 percent.

Q. And how does Lialda's current market share of 37.3 percent compare to your other competitors?

A. That market share number is approaching the combination of the next three competitors' market shares combined.

Q. And do you know what Lialda's gross sales were in 2015?

THE COURT: Let me ask a question, if I might, if that's all right with you folks.

MR. HAUG: Yes.

THE COURT: When you say 37.3 percent of the market, how are you defining the market? Are you defining that as the market for Lialda's drugs?

THE WITNESS: So the market are those drugs that

I outlined before --

THE COURT: The four drugs plus Lialda?

THE WITNESS: Yes. It's the mesalamine drugs plus Colazal, plus Dipentum. Both of those are pro drugs.

THE COURT: All right. Thank you.

MR. HAUG: Thank you.

BY MR. HAUG:

Q. What is a pro drug, very briefly?

A. A pro drug is -- and, again, I'm not an expert in this field, but my understanding of a pro drug, it's a chemical and active ingredient, or chemical that is ingested into the body in one form and then catalyzed into the active ingredient that actually treats the condition while inside the body. And Dipentum and Colazal do that in the large intestine.

Q. And I was starting to ask you the question. What were Lialda's gross sales in 2015, if you know?

A. In 2015, for the first time, Lialda had gross sales in excess of $1 billion. And that was after reaching $870 million in 2014.

Q. Do you recall what the sales were in 2013?

A. In 2013, the sales were, I think, $660 million.

MR. HAUG: No further questions.

THE COURT: Cross-examination.

MR. MURPHY: Good afternoon, Your Honor.

CROSS-EXAMINATION

BY MR. MILLER:

Q. Good morning, Mr. Stautberg. Nice to see you again.

A. Nice to see you again.

THE COURT: Can you identify yourself for the record?

MR. MILLER: Andy Miller from Locke Lord.

THE COURT: All right. Thank you.

BY MR. MILLER:

Q. Just a few questions, Mr. Stautberg. You mentioned a competitive environment of Lialda's and you said that when, correct me if I'm wrong, when Lialda all came on the market, Asacol was on the market a year?

A. That's correct.

Q. That is Asacol 400 milligrams; is that correct?

A. That's correct.

Q. And Asacol 400 milligrams, that was discontinued from the market; is that correct?

A. The manufacturer of Asacol 400 withdrew, or technically, they stopped manufacturing and making available that product in 2013.

Q. And as a result of that discontinuation, Lialda did gain some market share; is that correct?

A. Lialda gained market share in 2013. It's difficult

to draw the direct tie, if you want to say it's because of the withdrawal of Asacol 400 from the market. The way I would characterize it is, there were a lot of patients who, when that product was discontinued, needed to be treated with other therapies.

A lot of doctors prescribed habitually in this category, and that forced doctors to think about what they were doing. When they thought about what they were doing, then they chose Lialda more than they had in a situation where Asacol was an option. And our market share grew as a result of that.

Q. And you're not here offering any opinion on the compositions of the '720 patent; is that correct?

A. That is correct.

MR. MILLER: No further questions, Your Honor.

THE COURT: All right. Any redirect?

MR. HAUG: No, Your Honor.

THE COURT: All right. Thanks very much, sir. You may step down.

THE WITNESS: Okay. Thank you.

(Witness excused.)

THE COURT: Your next witness?

MR. HAUG: Our next witness will be Vivian Gray, and my partner, Elizabeth Murphy, will conduct the examination.

THE COURT: All right. Thank you.

... VIVIAN ALBERTINA GRAY, having been duly sworn as a witness, was examined and testified as follows...

MS. MURPHY: Your Honor, may I approach the bench?

THE COURT: You may.

(Ms. Murphy handed binders to the Court.)

MS. MURPHY: May I approach the witness?

THE COURT: You may freely approach. Thank you.

(Ms. Murphy handed a binder to the witness.)

MS. MURPHY: Your Honor, Elizabeth Murphy, Frommer, Lawrence & Haug.

THE COURT: Thank you. You may proceed, Ms. Murphy.

DIRECT EXAMINATION

BY MS. MURPHY:

Q. Good morning, Ms. Gray.

A. Good morning.

Q. Can you please briefly describe for the Court your educational and professional background?

A. Yes. I received my Bachelor of Science degree with a major in chemistry from Mary Washington College at the University of Virginia.

Q. And your professional experience after that?

A. Yes. My professional experience in the area of dissolution started when I started working for the USP,

United States Pharmacopeia. I worked there for 23 years in various positions.

My first position for the first eight years was as a bench chemist doing dissolution testing. And the second eight years was method of, supervising method development for dissolution testing. And then the third eight years was as a liaison, which my job was to interact with the expert committees on dissolution and FDA and pharmaceutical industry.

Q. And do you currently serve on any professional committees?

A. Oh, I didn't finish. I'm sorry.

Q. All right.

A. I went -- from USP, I went to DuPont Merck and headed up their analytical dissolution group in their R&D department. And after that, in 2001, I began my consulting business for dissolution. The business was called V. A. Gray Consulting. And also I became managing director of "Dissolution Technology," which is a peer-reviewed journal on dissolution. And I have, I have nearly 40 years of experience in dissolution testing.

Q. And do you serve on any professional committees?

A. Yes, I do. I serve on quite a few committees. Mainly, the USP committee. USP. Mainly, one of the biggest and best committees is the USP Expert Committee on

pharmaceutical dosage forms. That is the committee at USP that approves standards for dissolution testing, and that is an elected position.

Q. And in what capacity do you serve on the expert committee?

A. On the expert committees, we make decisions about general chapters and monographs and dissolution. We either revise general chapters or create general chapters. One of my roles on that committee, I was the author, co-author of two general chapters regarding dissolution, 1092 method development and validation, and then 1094, dissolution, special considerations for capsules.

Q. And who relies on these USP monographs and chapters you've just described?

A. The pharmaceutical industry, FDA, also other countries that cite the USP and their laws.

Q. And have you previously testified as an expert at trial?

A. Yes, I have. Salix v Novell.

Q. And did the Court accept you as an expert in that case?

A. Yes, they accepted me as an expert in dissolution testing.

THE COURT: Let me ask a question, if I might, Ms. Murphy.

You referenced USP a few times and gave me the name of it, United States Pharmacopeia I think you said.

THE WITNESS: Yes.

THE COURT: Can you tell me what that is?

THE WITNESS: Exactly. It is the United States Pharmacopeia. It is a nonprofit standard setting organization for the pharmaceutical industry. Its product is a large book called the USP. And this organization, first off, produces the USP. The USP have these standards that either are in monograph form or in general chapter form. And the standards are what the FDA uses to enforce the standard. In other words, the USP makes the standards and the FDA enforces these standards.

THE COURT: Thank you very much. Thank you.

MS. MURPHY: If we could please pull up PTX-543.

BY MS. MURPHY:

Q. And if you could turn to PTX-543 in your binder, Ms. Gray.

A. Actually in my binder, it's 544. That's okay.

Q. I believe we put PTX-543 up on the screen. Do you see that?

A. That's my CV.

Q. Okay. And is it accurate and up-to-date?

A. Yes, it is. I do have a couple of articles I just published which aren't in that CV.

MS. MURPHY: Plaintiffs would offer PTX-543 into evidence.

MR. MILLER: No objection, Your Honor.

THE COURT: It's admitted without objection.

(PTX-543 is admitted into evidence.)

MS. MURPHY: And plaintiffs would also offer Ms. Gray as an expert in dissolution testing.

MR. MILLER: No objection, Your Honor.

THE COURT: All right.

BY MS. MURPHY:

Q. Ms. Gray, can you please provide a brief description of what you have been asked to do for purposes of this litigation?

A. Yes. I have been asked to design and carry out experiments, dissolution testing on the Zydus -- three tablets of the Zydus product which include generating mesalamine dissolution data and also capturing digital images of the dissolution.

Q. And can you please describe for the Court briefly the experimental setup of your experiment?

A. Yes, I can. I have a schematic up there.

This is the USP Apparatus II dissolution paddles. You can see paddles there in the equipment.

This equipment has been, was equipment I used that was calibrated by, calibrated according to GMP

standards. This equipment, you can see there are eight vessels in the equipment. However, we only used three vessels, one for each.

THE COURT: What is a GMP?

THE WITNESS: Good manufacturing practice.

THE COURT: Thank you.

BY MS. MURPHY:

Q. And it looks like there is liquid in three of those vessels.

A. Yes.

Q. Is that what you were referring to?

A. Yes. It turns out that, let me just describe what is going on with those vessels.

There is a tablet in each vessel. There is the paddle that provides gentle agitation. Then you have the media, which I will describe later, three different media. And the bath is, the dissolution tester, that water bath there is set at 37 degrees centigrade body temperature.

What you don't see there are three cameras, a camera for each vessel. And that camera was mounted on a tripod and took images of the three different vessels at certain time intervals.

Also, there were lights around the setup to facilitate clearer imaging.

Q. Did you consider any materials to design your

dissolution experiment?

A. Yes, I did. I considered the validation report from the Zydus ANDA.

Q. If we could please turn to PTX-544. It's in your binder.

A. Okay.

Q. And, Ms. Gray, do you recognize this document?

A. Yes, it is. This is the method development report for the Zydus product. I relied on this report for my own experimental design.

Q. And why did you rely on this report for your experimental design?

A. Well, this was filed -- this was Zydus's, part of Zydus's ANDA which was filed with the FDA, which assured me of the fact that this was an accurate method that would produce accurate results.

Q. And if you could please turn to page 3 of this document which is marked PTX-544.3 at the bottom.

A. Okay.

Q. Do you see where it says "test methodology?"

A. Yes. Here is where there are three media used in the testing I described.

The first media is .1 normal hydrochloric acid.

The next media is 6.4 pH phosphate buffer.

And the third media is 7.2 pH phosphate buffer.

Q. Ms. Gray, when you say "phosphate buffer," what is phosphate buffer?

A. It's a dissolution media that is used very often in dissolution, because you see the pH there is 7.2, 6.4, and the acid is acid which is the pH of the stomach. And the intestinal tract shows the pH of 6.4 and 7.2. So it is a typical dissolution media, related to the body.

THE COURT: Is there some difference between phosphate and phosphate buffer?

THE WITNESS: It should be phosphate buffer.

THE COURT: All right. Thank you.

BY MS. MURPHY:

Q. And did you use these three media in your experiment?

A. Yes, I did.

MS. MURPHY: If we could please turn back to the schematic at PDX-3.2. I am sorry. 3.1.

BY MS. MURPHY:

Q. Ms. Gray, how are the dissolution measurements taken in your experiment?

A. Well, with each of these three vessels, a sample was taken from each at the specified time points. The sample was taken. It was a 10 mil aliquot. It was filtered and collected in a test-tube and then analyzed by UV spectrophotometry, generating absorbance values which was used to generate the percent dissolved.

Q. For each vessel, how much dissolution measurements were taken during your experiment?
A. 32 points.
Q. How do you know that?
A. Well, I have prepared a table that gives all these.
Q. Okay. And we have up on the screen, PDX-3.2. Do you see that?
A. Yes.
Q. Is that the table you prepared?
A. Yes, it is.
Q. Looking on the left-hand column, under dissolution media, what is shown under that column?
A. First off, this table is the dissolution data for tablet 1. And under the dissolution media, there is the acids, acid media, .1 normal HCl, and the phosphate buffer, pH 6.4, and the pH 7.2 phosphate buffer.
Q. And how many dissolution measurements were taken during the acid stage of your experiment?
A. There were two taken every 60 minutes with a total of -- the total time in acid was two hours.
Q. How many measurements were taken on the pH 6.4 phosphate buffer stage?
A. There were two taken. They were taken every 30 minutes for a total of one hour.
Q. And how many measurements were taken during the pH

7.2 phosphate buffer stage?

A. This, the samples were taken every 15 minutes for the first six hours and every 30 minutes for the last two hours. This was a total of eight hours. And there were 28 time points for the 7.2 phosphate buffer stage, totalling in all the 32.

MS. MURPHY: If we could turn to the next slide, please.

BY MS. MURPHY:

Q. PDX-3.3. Do you have that?

A. Yes.

Q. And what is shown here?

A. This says the very same information you saw with tablet 1 except for the percent dissolved is unique to tablet 2.

Q. And tablet 2 would be in vessel 2?

A. Yes.

MS. MURPHY: And if we could have the next slide, please.

BY MS. MURPHY:

Q. What is shown here?

A. This is the dissolution data on tablet 3. This, all this description of the experiment is identical to tablet 2 and 1 except the dissolution of the percent dissolution dissolved is unique to tablet 3.

Q. And tablet 3 is the vessel 3; is that right?
A. Yes.
THE COURT: Can you tell me how you get more than 100 percent dissolution?
THE WITNESS: This is not unusual to see that in dissolution. It's simply can be that the measurement is showing that it was manufactured to slightly above 100 percent. It's, we see this all the time. And, in other words, it is very rare that you would actually see 100.00 all with the labeled claim.
THE COURT: So what it is reflecting is that the amount of what?
THE WITNESS: The active ingredient.
THE COURT: The active ingredient is above the amount that was supposed going to be in it.
THE WITNESS: Slightly, yes. But it's typical variation, typical balance of data for 100 percent dissolved.
THE COURT: All right. Thank you.
MS. MURPHY: If we could please turn to PTX-547-R.
BY MS. MURPHY:
Q. Ms. Gray, do you recognize this document?
A. Yes. This is the Boston Analytical report of the dissolution data that was generated in my experiment.
Q. And who is Boston Analytical?

A. It's a contract lab that I supervise doing this dissolution testing. I had previous experience with this lab from several projects.

Q. Okay. And if you could please turn to the page number 5 which is marked PTX-547-R-4.5.

A. (Witness complies.)

Q. Are you there?

A. Yes.

Q. Do you see table 6 on that page?

A. Yes, I do. This is the report of the dissolution results for the three vessels, going over to the next two pages all the way to the end of the experiment, to 480 minutes.

Q. Where do you see the end of the experiment on these pages.

A. It's on PTX-547-R.7.

Q. And the average percent dissolved in this column, do you see on the right-hand side, there was average percent dissolved?

A. Yes.

Q. What is that?

A. That is -- well, first off, vessels 1, 2, and 3 were, the percent dissolved were calculated for that particular time point and the average in vessel 1 is the average of the three. No, that's just the median of the calculation.

Q. For each time point?
A. Yes.
Q. Okay. And did you check the data that we have been looking at in table 6 for accuracy?
A. Yes, I did.
Q. How did you do that?
A. I referred to, first off, there is a sample calculation on R 9, R.9. And then I used the raw data in, that is shown in R. Let's see. I am not sure of this, it has a page number. But if you, right after R., it must be R.11, 12, 13, 14. Let's see. Go to the very end there. To page, page R.19. No, R.20. And I used this raw data to calculate the percent dissolved.
Q. And can you turn to the next page, PTX-547-R.21?
A. Yes, I have it.
Q. And what is shown there?
A. This is the notebook of where the analysts wrote down their observations and experimental information.
Q. Okay.
A. This, by the way, this notebook page was witnessed by their supervisor at the bottom.
MS. MURPHY: I would offer PTX-547-R into evidence.
MR. MILLER: No objection.
THE COURT: All right. Exhibit 547-R, which I

take it is the entirety of that exhibit, is admitted without objection.

(PTX-547-R is admitted into evidence.)

BY MS. MURPHY:

Q. And if you could please turn to the tab marked PTX-900.1053 in your binder?

A. Yes. Oops. Yes. Okay.

Q. And just looking at that page, PTX-900.1053, what is that? Rather, do you recognize this document?

A. Yes, I do.

Q. What is shown there?

A. This is the mean value of the percent dissolved. This is a graphical representation of a mean value of the percent dissolved. The dissolution data.

MS. MURPHY: And plaintiffs would offer PTX-900.1053 into evidence.

MR. MILLER: No objection, Your Honor.

THE COURT: It is admitted without objection.

(PTX-900.1053 is admitted into evidence.)

BY MS. MURPHY:

Q. Ms. Gray, we just talked about the dissolution data during your experiment. I'd like to turn to the images that you took of the tablets in dissolution. If we can please put up the schematic we were looking at before, PDX-3.1.

Could you please explain how the images were

captured during your experiment?
A. Yes. As you recall, there are three vessels with the three tablets. Each had a camera. The camera was put on a tripod and operated by remote control. And so there were images taken for every, many times, all at set time intervals; and also the images contained a date stamp, date and timestamp, and also a number, an image number.
Q. Okay. And what were the time intervals?
A. I have a table that I prepared that I can tell you that.
Q. Could you turn to PDX-3.5?
A. (Witness complies.)
Q. Is this the table you prepared?
A. Yes. And this is a table of the information about the photos for tablet 1 and vessel 1.
Q. Okay. And how many time intervals did you take pictures for in the acid stage?
A. Four. The approximate times for these photographs were: within one minute, five minutes, 60 minutes and 120 minutes.
Q. And what were the intervals for the pH 6.4 phosphate buffer stage?
A. This was also within one minute, five minutes, 30 minutes, and 60 minutes.
Q. And same question for the pH 7.2 phosphate buffer

stage?
A. It was within one minute, then every three minutes for the first two hours, and then every ten minutes for remaining six hours.
Q. And then, Ms. Gray, what was the total length of your experiment in terms of hours?
A. It was 11 hours, and I supervised the experiment, the capture of the pictures, and also the dissolution for that entire time.
Q. And looking at the next column, titled d1v1, do you see that?
A. Yes.
Q. What is that?
A. The d1v1 is the designation for vessel 1.
Q. Okay. Why are there several values reported for each of these time points?
A. Under d1v1, it goes from 0.10 to 0.13, and that is how many images, the number of the images that were taken during that time, during that one minute.
Q. Okay. And if we could go onto the next column time. Do you see that?
A. Yes.
Q. What does that refer to?
A. That refers to the hour, minutes and seconds corresponding to the image number in the previous column.

Q. And the d1v1 column and the time column, I think you mentioned earlier that there were image and time stamps on each of the photos taken. Do those refer to those image and time stamps?

A. Yes. This d1v1 is designated for all the images in vessel 1 and the designation of d1v2 is for all the images taken in vessel 2, and d1v3 is for all the images taken in vessel 3. And the time stamp includes the time, the hours, minutes and seconds.

Q. And the last column on the far right entitled PTX, do you see that?

A. Yes.

Q. What does that refer to?

A. That refers to the number that was given to each recorded, that was recorded for each image.

Q. And if you could please turn to PTX-900.18 in your binder. Are you there?

A. Yes.

Q. Do you recognize this image?

A. Yes. It's the very first image taken in vessel 1 of the whole experiment, in acid stage.

Q. I see on the bottom right-hand corner, there's an insignia, D11-0010. Is that the image stamp you were talking about before?

A. Yes.

Q. Below that, there's a date and a time stamp? Do you see that?
A. Yes.
Q. Is that the date and time stamp on the table?
A. Yes.
Q. This is the first image of the acid stage. Can you identify by PTX number the last image taken in the acid stage of your experiment?
A. Let's see. That's chart -- you want the last image for the acid stage?
Q. The last image for the acid stage for vessel 1?
A. Okay. 900.37, and leaping over to 900.37. Yes. And I have that.
Q. So what is the range of images by PTX number for all of the images taken during the acid stage for vessel 1 in your experiment?
A. It goes from PTX-900.18 to PTX-900.37.
Q. Okay. And if you could turn to the next page, PTX-900.38.
A. Mm-hmm.
Q. Do you recognize this image?
A. Yes. This is the very first image within, taken within one minute of the 6.4 phosphate buffer stage.
Q. And which vessel is this for?
A. This is for vessel 1.

Q. All right. And, again, could I ask you to identify the last image taken during the pH 6.4 phosphate buffer stage?

A. That is 900.66. I have it.

Q. And, Ms. Gray, what is the PTX number range for all of the images of the Zydus tablet taken from vessel 1 during pH 6.4 phosphate buffer stage in your experiment?

A. 900.38 to 900.66.

Q. Okay. And if we could go to the next image, which is marked PTX-900.67.

A. Yes.

Q. And --

A. This is the first image taken within one minute of vessel 1 in the 7.2 phosphate buffer stage.

Q. All right. And, again, could you identify for me by PTX number the range of images taken during the pH 7.2 phosphate buffer stage?

A. 900.67 to 900.362.

Q. All right. And --

A. Do you see that? Do you see that?

Q. Can we pull up PTX-900.362?

A. Yes.

Q. All right.

A. And that's the last image of vessel 1.

MS. MURPHY: Plaintiffs would move into evidence

PTX-900.18 to PTX-900.362.

MR. MILLER: No objection, Your Honor.

THE COURT: It's admitted without objection.

(PTX-900.18 to PTX-900.362 were admitted into evidence.)

BY MS. MURPHY:

Q. Okay. And if we can please go to slide 6. What is shown here?

A. This is the slide prepared for the photos for tablet 2 and vessel 2. This contains at least for the first two columns the same information that you saw in the previous table, but it contains the image numbers, the time and the PTX numbers for vessel 2, or tablet 2.

Q. All right. And if we go to PTX-900.402.

A. Yes.

Q. All right.

A. And this is, this is the first image taken within one minute of vessel 2 in the acid stage.

Q. And can you identify the range of images by PTX-number?

A. It begins with 900.402 and ends with 900.419.

Q. And what is the stage of your experiment that those images correspond to for vessel 2?

A. That would be acid stage.

Q. Okay. And if we can go to PTX-900.420.

A. Yes.

Q. What is shown here?
A. This is, this is the, for vessel 2, it is the first image taken within one minute of pH 6.4 phosphate buffer stage.
Q. And what is the PTX number range for all of the images taken during the pH 6.4 phosphate buffer stage for vessel 2?
A. 900.420 to 900.441.
Q. Okay. And if we could turn to PTX-900.442.
A. Okay. Excuse me. Okay.
Q. And --
A. This is, this is the first image taken for vessel 2 within one minute in the 7.2 phosphate buffer state.
Q. And what is the range of images by PTX number for pH 7.2 phosphate buffer state for vessel 2?
A. It goes from 900.442 to 900.722.
Q. Okay. And if we could turn to the next and last slide, which is PDX 3.7.

Ms. Gray, what is shown here?

A. This is a table, Table 3 -- this is the table for tablet 3 and vessel 3, describes the photos taken during the run. The dissolution media and photo time points are the same, but the D1, D3 and the time and the PTX numbers are unique to tablet 3.
Q. And, Ms. Gray, could you please read the range of PTX

numbers for all photos taken during the acid stage?

A. 900.736 to 900.756.

Q. And this is for vessel 3; is that right?

A. Vessel 3, yes.

Q. Okay. And, Ms. Gray, for vessel 3, could you please read the range of PTX numbers for images taken during pH 6.4 phosphate buffer stage of your experiment?

A. Yes. 900.757 to 900.775.

Q. And could you also please read the PTX number range for all of the images taken in vessel 3 for the pH 7.2 phosphate buffer stage?

A. 900.776 to 900.1052.

MS. MURPHY: And plaintiffs would offer into evidence PTX-900.736 to 900.1052.

MR. MILLER: No objection, Your Honor.

MS. MURPHY: And if we could go back one slide, please.

THE COURT: It's admitted.

MS. MURPHY: My apologies. I'm sorry Your Honor.

(Exhibit admitted into evidence.)

BY MS. MURPHY:

Q. We were looking at the data before. This is for vessel 2; is that right?

A. Okay.

Q. Okay. And plaintiffs would additionally offer into evidence PTX-900.402 to PTX-900.722.

MR. MILLER: No objection, Your Honor.

THE COURT: Admitted without objection.

(Exhibit admitted into evidence.)

BY MS. MURPHY:

Q. Ms. Gray, we've just gone through the details of your experiment that you performed for this case, including the measurements, the dissolution measurements that you took and the images that were taken of the three vessels.

Do you have an opinion as to whether the data and images that we've gone through were an accurate representation of the Zydus product?

A. Yes. The data we have just gone through is an accurate are representation of the dissolution of the Zydus product.

MS. MURPHY: Thank you, Ms. Gray. No further questions.

THE COURT: Cross-examination.

MR. MILLER: Thank you, Your Honor. Andy Miller again for defendants.

CROSS-EXAMINATION

BY MR. MILLER:

Q. Ms. Gray, you don't have any opinions in this case on infringement; is that right?

A. No, I do not.
Q. And the only ingredient as it were that you analyzed in the Zydus product is mesalamine; is that correct?
A. Yes.
MR. MILLER: No further questions, Your Honor.
THE COURT: All right. Thank you.
Any redirect?
MS. MURPHY: No, Your Honor.
THE COURT: All right. Thank you, ma'am. You may step down.
(Witness excused.)
THE COURT: Hold on just a moment.
Ms. Farnan?
MS. FARNAN: Your Honor, I wanted to let you know that the next witness is going to be a video deposition that is going to take an hour, so I didn't know if Your Honor wanted to take a break at this point.
THE COURT: Not really.
MS. FARNAN: All right. We're happy to proceed then.
THE COURT: Let's fire it up and go.
MS. FARNAN: Shire is now calling defendant's 30(b)(6) witness, Mr. Kulkarni, by video deposition.
Among other things, he was designated as a 30(b)(6) witness on the composition, formulation and

development of the Zydus ANDA. Product and I will get some binders to hand up for Your Honor.

THE COURT: All right. Hold on just a moment.

Mr. Gaertner?

MR. GAERTNER: Yes, Your Honor. This is the issue that I think Mr. Haug graciously flagged at the beginning, that is the dispute over whether or not this is a 30(b)(6) deposition. I will tell you why that is.

THE COURT: Okay.

MR. GAERTNER: In advance of this deposition, as it often happens in a 30(b)(6), you try to negotiate. You file objections on the topic and you negotiate the scope of them and you reach an agreement. Then you let it go.

What happened here was the plaintiffs noticed this witness both as a 30(b)(1) and a 30(b)(6) deposition witness. We objected to the 30(b)(6) topics. We endeavored to reach an agreement on those 30(b)(6) topics.

We did not reach an agreement on those 30(b)(6) topics, so at the time at the time the deposition went forward, we still objected to those. And we made objections on the record during the deposition. However, we did not refuse to let the witness answer because we know we're not allowed to do that, plus he was a 30(b)(1) witness.

But we do object to having him characterized as a 30(b)(6) witness on these various topics, because we had

an objection standing. We made it clear we were not presenting him on that basis.

THE COURT: Did you agree on him being a 30(b)(6) witness on any topic?

MR. GAERTNER: Not to this topic, no.

THE COURT: No. When you say "this topic," there's nothing that this man is going to say that you agree he is a valid 30(b)(6) witness that could bind Zydus?

MR. GAERTNER: We went back and looked at the transcript last evening when this when this issue came to a head. We went back.

I noticed we objected during the time at the deposition to each of the topics that the plaintiffs tried to characterize as 30(b)(6) topics because we had objections pending and we hadn't reached a resolution of this.

THE COURT: Right. So the answer to my question is yes?

MR. GAERTNER: Yes, it is.

THE COURT: There's nothing that this man says that you agree could bind the defendant --

MR. GAERTNER: That's correct.

THE COURT: -- as a 30(b)(6) witness. All right. All right. I got your position.

Ms. Farnan, are you going to speak to this?

MS. FARNAN: Yes, Your Honor. I'm speaking to this because I was involved in the meet and confers we had on this last evening.

The issue here is just whether or not it's testimony that is binding on the company. And he was offered as a 30(b)(6) witness. He appeared as a 30(b)(6) witness. And they are correct, that there were some objections to the topic, but it was not a complete objection.

So, for example, in -- and on page 20 of his deposition transcript, the objection was --

THE COURT: Hold on just a moment. If you are going to be referring to that, why don't you hand up the transcript.

MS. FARNAN: Your Honor, may I approach?

THE COURT: Please.

(Ms. Farnan handed binders to the Court.)

THE COURT: Thank you. Okay. You started to refer to --

MS. FARNAN: So if you look, Your Honor, in the front of the binder -- and I just want to note, we did have this dispute last night and we asked them to -- Your Honor will see when we go through the designations that there is no specific objection to scope as to the specific questions that we are seeking to admit into evidence, so

there's only this general objection at the beginning of the deposition.

And last night we asked them to identify, which of these portions of testimony do you say are outside the scope, and they wouldn't identify it. So I think that's one area. We can put that aside and I can show Your Honor where they, in fact, agreed. He was presented on some of these important topics subject to their objection.

So we'll look at page 20 of his transcript. And what's going on here is that Shire is reading into the record the topic and asking if he's prepared to testify on them.

And on line 5 on page 20, it says, so he's being presented on topic one as limited by a response and objection.

So, of course, there were objections that were served, but they did agree to, for example, produce him on topic one.

Another topic that we think is important here, but they have not identified it, would be topic six. And if you look at page 25 of the transcript, line 7 to 11, he says, again, object to the extent that Mr. Lief is implying that the witness is presented on full scope of topic six as it was worded as he is not being presented on that full scope.

So it was clear at the deposition, and it was clear from their objection that he was a 30(b)(6) witness, but that they were attempting to limit it. But there's no specific objection to any of the questions then later.

And I think what they are trying to do is say, we don't want this testimony binding on the company. But not only is he a 30(b)(6) witness, but under 801(c)(2), as an officer, managing agent, who dealt with formulation in the course of his business, these are binding admissions on the company in any event.

So it's not really clear to us how they're going to walk away from the binding nature of this, nor have they identified it. But he was clearly offered as a 30(b)(6) witness. They had some objections. Their primary objection was that we would be talking about the current ANDA formulation, which we did. We have not heard anything to say that this testimony applies to anything other than the current Zydus product.

And so we think we are well within the scope of the 30(b)(6) on which they offered this witness, and it's our view that all of this testimony is therefore binding on the company.

THE COURT: Okay. Thank you.

Mr. Gaertner, your response?

MR. GAERTNER: At the beginning of the deposition, the examination started out with reviewing each of the deposition topics. I rendered objections to each of those topics, but I certainly --

THE COURT: Let me stop and ask you this.

MR. GAERTNER: Yes.

THE COURT: They sent you a 30(b)(6) notice and you offered this gentleman. Is that Mr. Kulkarni? Is that the man you put forward to be the representative? Even if you thought we're going to negotiate the scope, he is the guy you put forward. Is that correct?

MR. GAERTNER: That's correct, Your Honor.

THE COURT: All right. So how is it that we get into the courtroom on the day of trial and you are prepared to say, there's nothing he's saying that would be an appropriate 30(b)(6) binding admission?

Was the testimony so outside the scope of what they had suggested they wanted a witness for the company about, that it would be unfair to view him as an appropriate representative for the company?

MR. GAERTNER: It depends on the question, Your Honor. It does.

THE COURT: All right. So I hear Ms. Farnan saying, well, they never said anything as they were going through as to any question that they thought was beyond the

scope of the appropriate level of questioning for this person.

Is that an accurate representation?

MR. GAERTNER: I think in general, it is, Your Honor.

THE COURT: Okay.

MR. GAERTNER: And we rendered the objection at the beginning, but that's right. As we went along, we did not.

THE COURT: You know what, I don't have to make a decision right now at this point and I'm not going to.

I will say that as a general matter, I'm unimpressed with the sort of general blanket statement that a 30(b)(6) witness that you offered somebody who can't bind the company in any way, even though you did not point out at any point specifically, he can't talk about that for the following reasons. That's an unimpressive and unpersuasive position.

But I don't have to make my mind up about it now. I will let you guys fight it out as we get to post-trial briefing and findings of fact and conclusions of law. If you want to take a stand or you want to try to persuade me, now, wait a second, that's just not fair, I'm not telling you that you can't do that. I'm just giving you

a general heads-up that it does not move me very much, Mr. Gaertner.

MR. GAERTNER: Thank you, Your Honor.

THE COURT: So let's go ahead and play it.

MS. FARNAN: Your Honor, I may I approach with the remainder of the binders for this witness?

THE COURT: Yes.

(Ms. Farnan handed binders handed to the Court.)

MS. FARNAN: Your Honor, as I indicated, this will be testimony by video.

THE COURT: All right. Before we start, I wanted to say this. If you need a break at some point, I'm prepared to go through this and break, but if you want to break sooner, give me a sign.

All right. Good. Good enough. Thanks.

(The videotaped deposition of Sushrut Krishnaji Kulkarni was played as follows.)

"Sushrut Krishnaji Kulkarni having been first duly affirmed, was examined and testified as follows:

"Question: Could you state your full name for the record.

"Answer: Sushrut, Krishnaji Kulkarni.

"Question: And do you have any residences in the United States?

"Answer: No.

"Question: Okay. And what is your current title at Zydus?

"Answer: Senior -- senior vice president.

"Question: And are you senior vice president of any particular department?

"Answer: I'm head of PTC. Is the Pharmaceutical Technology Centre.

"Question: Okay. And how long have you had that position?

"Answer: Since November 2012.

"Question: And what are your responsibilities in that position?

"Answer: I am responsible for all development activities which are carried out in this development center.

"Question: Okay. And were you involved continuously from 2007 or -- until September of 2012 with the Lialda project?

"Answer: Initially, I was directly involved for up to 2009 or 2010, probably. Then it was a supervisory role.

"Question: Okay. And did your involvement in those years relate to coming up with the formulation for Zydus's generic version of Lialda?

"Answer: Yes.

"Question: Okay. And then when you returned to

Zydus in November of 2012, did you continue to be involved in the generic Lialda project at Zydus?

"Answer: At a supervisory level.

"Question: And does that remain the case to this day?

"Answer: Yes.

"Question: All right. I take it you understand that you're here today as a 30(b)(6) deponent on behalf of the defendants, Zydus and Zydus Cadila?

"Answer: Yes.

"Question: Do you have any personal knowledge of the '720 patent?

"Answer: No.

"Question: Have you ever seen it?

"Answer: Yes.

"Question: Do you recall the first time you ever saw the '720 patent?

"Answer: I don't remember exactly. Probably 2007 somewhere.

"Mr. Lief: Let me mark as Kulkarni Exhibit 102 a document bearing Bates Nos. ZYDUS_MES2353657 through 235843.

"The Witness: Thank you.

"Mr. Lief: And let me also mark as Kulkarni Exhibit 103 a document bearing Bates Nos. ZYDUS-MES25337

through 25799.

"Question: With respect to Kulkarni Exhibit 102, have you seen this document before?

"Answer: Yes.

"Question: And can you tell me what this document is?

"Answer: This is a batch manufacturing record for EMM196.

"Question: If we turn and go forward to Bates page ZYDUS_MES235660. Do you have that page?

"Answer: Yes.

"Question: Can you tell me what is shown on this page?

"Answer: This is a manufacturing formula for EMM196.

"Question: Okay.

"Answer: First three steps.

"Question: And is this a list of the ingredients that are in EMM196, I guess continuing on to the next page, 235661.

"Answer: Yes.

"Question: Now, focusing on page 235660, I see there three headings. One heading says 'compaction,' one heading says 'granulation,' and one heading says 'lubrication.' Do you see that?

"Answer: Yes.

"Question: And what is the significance of each of those headings?

"Answer: These are the steps in manufacturing of EMM196.

"Question: Okay. And are those done in sequence? In other words, does the compaction step come before the granulation step, which then in turn comes before the lubrication step?

"Answer: Yes.

"Question: Okay. In the compaction step, underneath that heading, I see three ingredients listed. Do you see that?

"Answer: Yes.

"Question: And am I correct that those ingredients in the compaction step are mesalamine, colloidal silicon dioxide, AEROSIL-200 Pharma, and magnesium stearate?

"Answer: Yes.

"Question: Okay. Are any of those ingredients binders?

"Answer: No.

"Question:

"Mr. Lief: Okay. Why don't we mark as Kulkarni Exhibit No. 104 a document bearing Bates Nos. ZYDUS_MES23363 through 23422.

"Question: Now, looking at Kulkarni Exhibit 104, let me ask you, first of all, have you seen this document before?

"Answer: Yes.

"Question: Okay. Now, this document comes from -- am I correct -- comes from the ANDA submission that Zydus made for its generic version of Lialda before the EMM196 batch had been made; correct?

"Answer: Yes.

"Question: Okay. Is it your understanding that the statements made in this quality overall summary document for the earlier exhibit batch still apply to exhibit batch EMM196?

"Answer: Yes.

"Question: And then, again, in Exhibit Kulkarni 102, at page 235660, the next ingredient on the list for batch EMM196 is magnesium stearate.

"What is the function of magnesium stearate in row 3 there?

"Answer: Lubricant.

"Question: Okay. And what is your understanding of what a lubricant does?

"Answer: Improve the flow of powder.

"Question: Now, with respect to magnesium stearate as used here in row 3 for batch EMM196, do you know

whether it is hydrophobic?

"Answer: Yes.

"Question: Yes, it is?

"Answer: Yes.

"Question: What is your basis for saying it is not lipophilic?

"Answer: Magnesium stearate is hydrophobic because it repels water. And it is not lipophilic because it has not affinity towards lipid. That's my understanding.

"Question: Would you agree with me that in that first phase, the compaction phase, there are no hydrophilic materials?

"Answer: No.

"Question: No, you agree with me or --

"Answer: Yes.

"Question: -- no, you disagree with me?

"Answer: No hydrophilic material.

"Question: Okay.

"Answer: Except API. API, it's soluble in aqueous."

THE COURT: Can you stop that? Yes. Is it possible for you to just back that? Because I couldn't hear that last statement, that last answer.

"Question: Would you agree with me that in that first phase, the compaction phase, there are no hydrophilic

materials?

"Answer: No.

"Question: No, you agree with me or --

"Answer: Yes.

"Question: -- no, you disagree with me?

"Answer: No hydrophilic material.

"Question: Okay.

"Answer: Except API. API, it's soluble in aqueous.

THE COURT: Okay. Stop. And point me to the page because I am still having a hard time hearing his response.

What page are we on of the deposition at this point.

(The Court and court clerk confer.)

MR. LIEF: Your Honor we're told it's page 55.

No, maybe not. 52.

THE COURT: Okay. Thanks. Go ahead.

"Question: The mesalamine itself --

"Answer: Yeah.

"Question: -- is soluble in water?

"Answer: Yeah.

"Question: Okay. But the other two ingredients, colloidal silicon dioxide and magnesium stearate, are not hydrophilic to your understanding;

correct?

"Answer: Yes.

"Question: The next step says 'granulation' or the next title says 'granulation' I should say. And there are several ingredients listed under there.

"In row 4, it says 'carboxymethylcellulose sodium.' And then in parentheses, it says, '(Blanose CMC 7HF pH.)' Do you see that?"

"Answer: Yes.

"Question: With respect to that ingredient, carboxymethylcellulose sodium, what is its role in batch EMM196?

"Answer: This is a release retardant. It's a matrix former.

"Question: When you say 'release retardant', are you saying that chemical plays a role in controlling the release of the drug, mesalamine, from the tablet?

"Answer: Yes.

"Question: Okay. And it does that by forming a matrix within EMM196?

"Answer: Yes.

"Question: Okay. And is carboxymethylcellulose sodium a hydrophilic chemical in this product?

"Answer: In my opinion, it is hydrophilic material.

"Question: Going down to the next ingredient, which is "sodium starch glycolate type A (Glycolis/Roquette), what is the function of that ingredient in batch EMM196?"

"Answer: It is disintegrant.

"Question: Okay. And what is a disintegrant?

"Answer: Disintegrant is ingredient which helps to disintegrate the tablet.

"Question: Okay. In that sense, does it play a role in the rate of release of the drug from the product?

"Answer: Rate of release is a function of entire tablet.

"Question: Okay. So the answer is, yes, it does play a role?

"Answer: Yes.

"Question: And is sodium starch glycolate type A a hydrophilic material in this product?

"Answer: Yes.

"Question: Does microcrystalline cellulose play any role in retarding the release or slowing the release of mesalamine from the product that is EMM196?

"Answer: In my opinion, no, it does not.

"Question: Returning to the prior page, which is ZYDUS_MES235660. With respect to the three -- actually, the four chemicals that are listed below the heading 'granulation,' rows 4 through 7 -- carboxymethylcellulose

sodium, sodium starch glycolate type A, hypromellose 15 CPS and purified water -- are any of those chemicals hydrophobic?

"Answer: No.

"Question: Okay. Are any of those chemicals lipophilic?

"Answer: No.

"Question: How small are the particles, if you know, that come out of the oscillating granulator when EMM196 is made?

"Answer: I don't know. I don't have idea.

"Mr. Lief: Continuing in Kulkarni Exhibit 102. If we could turn to what is page ZYDUS_MES235695.

"Question: Do you have that?

"Answer: Yeah.

"Question: And do you see there's a Step No. 5.0 and then 5.1 shown on this page?

"Answer: Yeah.

"Question: Step 5.1 has a heading 'preparation of pre-mix,' and then there are various sub-steps that are described in there.

"Can you tell me what is being done in Step 5.1?

"Answer: This is a preparation of pre-mix for compaction.

"Question: Okay. And so is this the three

ingredients that are going to be put through the roll compactor?

"Answer: Yes.

"Question: Okay. And so that includes the mesalamine, the colloidal silicon dioxide, and the magnesium stearate?

"Answer: Yes.

"Question: And is it correct that those three ingredients are mixed together in what's called an 'egg shell blender?'

"Answer: Yes.

"Question: What is an 'egg shell blender?'

"Answer: It's a blender having the shape of egg shell, oval-shaped.

"Question: Okay. All right. And for how long are those three ingredients, how long were they mixed on this page for batch EMM196?

"Answer: It is for ten minutes.

"Question: Ten minutes. And what is the purpose of the mixing of those three ingredients?

"Answer: It's a uniform mixture of colloidal silicon dioxide and magnesium stearate.

"Question: And so it's to create a uniform mixture of those three ingredients together?

"Answer: To create a mixture, yeah.

"Question: All right. Turning back to Exhibit 102, which was, again, the current EMM196 batch.

The material -- the mesalamine, colloidal silicon dioxide, and magnesium stearate -- goes through the roll compactor with these settings?

"Answer: Excuse me. You're on which page?

"Question: I am sorry. I am on page ZYDUS_MES 235700.

"The materials -- the mesalamine, colloidal silicon dioxide and magnesium stearate -- go through the roll compactor, and then am I correct that material in Step 6.3.4 is then put through an oscillating granulator? Is that correct?

"Answer: Yes.

"Question: Okay. And the result that comes out of the oscillating granulator is granules; correct?

"Answer: Yes.

"Question: And the granules that come out of the oscillating granulator, what chemicals are in those granules?

"Answer: These are compacts of mesalamine.

"Question: Now, if we go to what is marked as ZYDUS_MES235716.

"Again, this is in Exhibit 102. There's a Step No. 10.0 here that has a heading: 'Granulation Lot A.' Do

you see that?

"Answer: Yes.

"Question: Okay. And then in Step 10.1, it says 'transfer.' Do you see that?

"Answer: Yeah.

"Question: And under 'transfer,' the first line reads, 'mesalamine compacted.' And then it says (Lot A of Step No. 9.0.)

"Do you see that?

"Answer: Yes.

"Question: Now, when it says 'mesalamine compacted,' am I correct that that's referring back to the compacted granules that have the mesalamine, silicon dioxide, and the magnesium stearate in them? Correct?

"Answer: Yes.

"Question: Okay. And then it reads in the next two lines, 'carboxymethylcellulose sodium and sodium starch glycolate' and then it says 'into the HSMG bowl.' Do you see that?

"Answer: Yes.

"Question: Okay. And so this is a step where you're taking the granules that were from the oscillating granulator and now adding on top of them these carboxymethylcellulose sodium and sodium starch glycolate materials in a new mixing bowl; correct?

"Answer: Yes.

"Question: Okay. Now, the granules that come out of this series of steps in Step 10, I guess 10.1, you know, and sub-steps of that, 10.1.2, those granules are bigger granules than the granules that came out of the oscillating granulator of the compacted mesalamine material; correct?

"Answer: Yes.

"Question: If you go to page ZYDUS_MES235722.

"Answer: Yeah.

"Question: Now, you have a Step 10.3, and it has a heading, 'milling.' Do you see that?

"Answer: Yeah.

"Question: Underneath that, there's a step 10.3.2. Do you see that?

"Answer: Yeah.

"Question: And that says:

"'Manually mix colloidal silicon dioxide with dried granules of Step No. 10.2.' And then it goes on.

"Do you see that?

"Answer: Yeah.

"Question: So the colloidal silicon dioxide that was used in that first compaction process doesn't find its way out of those granules to be a glidant in this later step?

"Answer: No.

"Question: And is that also true of the magnesium stearate that's used in the earlier compaction process?

"Answer: Yes.

"Question: Do you have, in your experience in formulation, do you have any recollection -- again, other than this formulation -- of using magnesium stearate as part of a compaction process at the beginning of the manufacturing process?

"Answer: I don't remember.

"Question: You have no recollection of that, as you sit here today?

"Answer: Yes.

"Question: If we go back to what we had marked as Exhibit 104, which is the quality overall summary from, really, the earlier batch, 345, as it was submitted, and as we discussed, it is your belief that this applies to 196 as well?

"Answer: Yes.

"Question: If we look at what is page ZYDUS_MES23378. At the bottom of that page, there's -- well, in the middle of the page, there's a table that compares the ingredients of the branded Lialda product with Zydus's proposed generic product; correct?

"Answer: Yeah.

"Question: And then below that table, there is a paragraph that reads:

"'Despite the apparent differences in composition between the proposed formulation and RLD, these differences are considered irrelevant in the context of having a potential effect with respect to therapeutic equivalence. This is based upon the noted similarities between the two products, both in terms of dosage form and dosage form design.' And it goes on. Close quote.

"Did I read that correctly?

"Answer: Yeah. Yes.

"Question: Okay. And is it your testimony that those statements are still true with respect to the new batch, EMM196?

"Answer: Yes.

"Question: If you turn, again, in Kulkarni Exhibit 104, to page ZYDUS_MES 23384.

"And with respect to, in the left-hand column, there's a, I guess I'll call it an oval towards the bottom that has -- it says 'magnesium stearate and AEROSIL-200.' Do you see that?

"Answer: Yeah.

"Question: Okay. And then there's an arrow from there that goes to an oval that says 'lubrication.'

Do you see that?

"Answer: Yes.

"Question: All right. And then from "lubrication,' there's two arrows, one that goes to 'tableting properties,' and one that goes to 'dissolution.' Do you see that?"

"Answer: Yes.

"Question: And what is your understanding of what that arrow that goes from 'lubrication' to 'dissolution' indicates with respect to EMM196?

"Answer: That's an error. That arrow is in error. This should have been from 'tableting properties.'

"Question: Okay. And do you have any reason to believe that the formulators who came up with the generic version of Lialda for Zydus did not review this page, ZYDUS_MES23384?

"Answer: That's an error which happened in this document.

"Question: Now, that was submitted at the same time that this quality overall summary was submitted; correct?

"Answer: Yeah. It's a part of the ANDA.

"Question: Okay. And subsequent to your deposition, though, where you first testified that this was an error, have you revised or amended the quality overall

summary to remove that arrow from 'lubrication' to 'dissolution.'

"Answer: No, we have not submitted.

"Question: Is there any reason you couldn't have done that? In other words, you couldn't have roll-compacted everything together in the first step, including the hydrophilic chemicals?

"Answer: It's a formulation strategy decided by a scientist --"

THE COURT: Can you stop that for a moment.

I just want to point out, this has been very helpful to have it highlighted in the transcript. That last piece was not highlighted. To the extent that you folks are intending to limit the record to what is highlighted, you are going to need to fix that because it looks like the last bit of testimony which appears on page 104 of the transcript was not highlighted.

MS. FARNAN: Your Honor, I think that was an oversight. That was an counter-counter designation.

THE COURT: Yes. However it got in. I am just trying to make -- you guys are building your record, right? Whatever you want to submit have in the record is fine with me within bounds of reason. I am just making clear that there is a piece that we just heard which is not highlighted in here, and when you are doing your setup of your proposed

findings of fact and conclusions of law, and I am looking at the record, I am just trying to avoid a dispute later on. Okay? Thanks. Go ahead.

"Question: And your understanding is the formulators preferred to have the first compaction step be only mesalamine, silicon dioxide, and the magnesium stearate?

"Answer: Yes:

Mr. Lief: All right. Let me mark as Kulkarni Exhibit 113 a document bearing Bates Nos. ZYDUS_MES239470 through 369518.

"Question: And with respect to this document, Kulkarni Exhibit 113, have you seen this document before?

"Answer: Yes.

"Question: Okay. And what is this document?

"Answer: This is the instruction manual for roll compactor.

"Question: Okay. And is this the roll compactor that was used in making EMM196 batch?

"Answer: Yes.

"Question: If you turn to what is page 369476, there is a page there that has the heading: 'Design of the machine and principle of operation.' Do you see that?

"Answer: Yes.

"Question: Okay. And the first sentence reads:

"This is a dry granulation method."

Did I read that correctly?

"Answer: That's -- I can't read.

"Question: That's correct?

"Answer: Yeah.

"Question: Okay. And do you agree with that, that roll compaction is a dry granulation method?

"Answer: Yeah, dry granulation can be done through roll compact.

"Question: Strike that.

"At the end of the Zydus process, in the compaction process, where you do the roll compactor and the oscillating granulator, do you get particles of different sizes?

"Answer: Yes.

"Question: And do you get, amongst those particle sizes, what would be called 'fines?'

"Answer: Yes.

"Question: If you look at the last sentence here on this page, it reads:

"'The addition of binders to the material being processed greatly reduces the production of fines.'

"Did I read that correctly?

"Answer: Which line are you referring to?

"Question: The very last sentence on page 369476.

"Answer: Yeah.

"Question: See that?

"Answer: Yeah.

"Question: Okay. Now, am I correct that in the roll compaction process that Zydus -- in the roll compaction process that Zydus undertook in EMM196 of the three ingredients that are included -- the mesalamine, the colloidal silicon dioxide and the magnesium stearate -- none of those are binders?

"Answer: Yes.

"Question: And so is it fair to say that, given this, this observation that the addition of binders reduces the production of fines, Zydus was not particularly trying to reduce the fines in the compaction step? Correct?

"Answer: Zydus's objective was to compact mesalamine. That's the objective with which we will undertake compaction.

"Question: Um-hmm. But you didn't have an objective to reduce fines?

"Answer: Our objective was to increase bulk density.

"Question: Irrespective of fines?

"Answer: Yeah.

"Mr. Lief: Let me mark as Kulkarni Exhibit 114 a document bearing Bates Nos. ZYDUS_MES 235643 through 235645.

"Question: And let me ask you, with respect to Kulkarni Exhibit 114, have you seen this document before?

"Answer: Yes.

"Question: And what is this document?

"Answer: It's a certificate of analysis of magnesium stearate from Cadila and from Dr. Paul Lohmann.

"Question: Who is Dr. Paul Lohmann?

"Answer: He is a supplier of magnesium stearate.

"Question: And is this the certificate of analysis for the magnesium stearate that is -- that was used in the exhibit batch EMM196 that Zydus has submitted to the FDA?

"Answer: Yes.

"Mr. Lief: Let me mark as -- let me mark as Kulkarni Exhibit 117 a document bearing Bates Nos. ZYDUS_MES212122 through 212135.

"Question: Okay. And in the trail of e-mails there -- in the trail of e-mails there, am I correct that you are both a recipient and a sender of various e-mails in this trail?

"Answer: Yes.

"Question: Okay. And if you look at the attachment, which begins at page 212125, and goes through page 212135, have you seen that document before?

"Answer: Yes.

"Question: Okay. And am I correct on the beginning page here, 212125, to this PowerPoint, the subject matter is: 'Mesalamine delayed release tablets, 1.2 grams?'

"Answer: Yes.

"Question: The e-mails that we're looking at are all -- look like July of 2009?

"Answer: Yes.

"Question: Okay. And so coming back to the PowerPoint that's attached to these e-mails, the next page of the document, page 212126, what is, what is on this page?

"Answer: These are Orange Book information for mesalamine DR tablets, 1.2 gram.

"Question: Now, if you go to the next page, which is ZYDUS_MES212127, there is a slide here that talks about 'MMX multi-matrix system' and then in parentheses it says (MMXTM technology) and it says 'background.' Do you see that?

"Answer: Yes.

"Question: And this reads, quote:

"'This new delivery system uses lipophilic and hydrophilic excipients enclosed within a pH dependent film coating that is resistant to gastric acid, thus delaying release of the drug until the tablet is exposed to a pH of 7 or higher (usually in the terminal ileum). When this film

disintegrates, intestinal fluids interact with the tablet, causing it to swell and creating an outer viscous gel mass. As the tablet passes through the colon, parts of the outer gel mass are expected to detach from the tablet core, releasing 5-ASA near to the colonic mucosa. The lipophilic excipient is interspersed with the tablet core and is thought to reduce the rate of 5-ASA dissolution by slowing the penetration of aqueous fluids."

"Did I read that correctly?

"Answer: Yes.

"Question: Okay. And this paragraph that I just read, is it fair to say that that is a summary by Zydus of the technology in the Orange Book patent?

"Answer: I really don't know from where it has been taken. Somebody -- some -- might be some from Internet or some, some other literature.

"Question: Okay. And with respect to the final product that Zydus is proposing for its generic version of Lialda, would it be a correct statement to say that it has 'a pH dependent film coating that is resistant to gastric acid?'

"Answer: Yes.

"Question: Okay. And would it also be a correct statement to say that when that film disintegrates from the Zydus product, 'intestinal fluids interact with the

tablet, causing it to swell' and create 'an outer viscous gel mass?'

"Answer: Yes.

"Question: Okay. And in that regard, with respect to the swelling, that derives from the presence of hydrophilic excipients in the proposed Zydus product; correct?

"Answer: Yes.

"Mr. Lief: All right. Let me mark as Kulkarni Exhibit 118 a document bearing Bates Nos. ZYDUS_MES263467 through 263473.

"Question: Looking at this document, Kulkarni 118, do you see that this is a trail of e-mails from around May and June of 2008?

"Answer: Yeah. Yes.

"Question: If you look at the bottom of page 263468, the last paragraph there, it talks about the 'OB patent (U.S. 6,773,720).' Do you see that?"

"Answer: Yes.

"Question: And that is the patent-in-suit in this case, the Orange Book patent; correct?

"Answer: Yes.

"Question: Okay. And in discussing that patent, it says the following:

"'The OB patent (U.S. 6,773,720) which is having

PCT filing June 2000 and granted on August 2004 in which it is mentioned a controlled release delayed release mesalazine (5-ASA) pharmaceutical composition. In the example, the given patent is mentioning the enteric coated formulation. The example also describes that the formulation release is delayed in gastric fluid. It claims 80 to 95 percent of the drug in the formulation along with the combination of hydrophilic and hydrophobic material to form the matrix."

"Did I read that correctly?

"Answer: Yes.

"Question: Do you recall, at this time at Zydus, people talking about the Orange Book patent as a patent that involved the combination of hydrophilic and hydrophobic chemicals?

"Answer: Yes.

"Mr. Lief: Let me mark as Kulkarni Exhibit 119 a document with Bates Nos. ZYDUS_MES266926 through 266933.

"Question: Okay. With respect to Kulkarni Exhibit 119, am I correct that this, on its first page, is a trail of e-mails during the January, early January 2008 period?

"Answer: Yes.

"Question: And am I correct that some of these e-mails are -- the bottom one seems to be to you? And then the top one, you send that and you forward it to Raju Satya;

correct?

"Answer: Yes.

"Question: And that top e-mail from you to Raju Satya on January 2nd, 2008, you write:

'Dear Dr. Raju,

'Attached below, please find formulation strategies of mesalamine DR tablets (1.2 gram) for your review.

"Regards, Sushrut Kulkarni.

"Did I read that correctly?

"Answer: Yes.

"Question: And then attached are several different formulation proposals for a -- I guess a generic version of Lialda; is that correct?

"Answer: Yes.

"Question: Okay. And after those, what looks like three pages, pages 266927 through 266929, where you have those formulations. Then starting on page 266930 through to the end, there seems to be a PowerPoint attached to that as well?

"Answer: Yes.

"Question: See that?

"Answer: Yeah.

"Question: Am I correct that amongst the ideas that were being contemplated at Zydus in this time period of

around January 2008 for ways to possibly get around the Orange Book patent, which is the patent-in-suit in this case, one of the thoughts was: We can have an inner hydrophobic matrix with an outer hydrophilic matrix, and that would circumvent the patent.

"Answer: Yes.

"Question: And so, for instance, if you look at page ZYDUS_MES 266933, there's a PowerPoint slide whose heading is: 'Formulation strategy to circumvent OB Patent No. U.S. 6,773,720 B1.'

"Do you see that?

"Answer: Yeah.

"Question: And amongst the strategies, number 2 says, the inner matrix is hydrophobic in nature instead of being lipophilic.

"Do you see that?

"Answer: Yes.

"Question: Now, in fact, what you've ultimately done in your -- in the product you're proposing to the FDA is, in fact, to have a hydrophobic material inside the granule surrounded by a hydrophilic material; correct?

"Answer: We have not done hydrophilic matrix. We have done -- we have used magnesium stearate as a lubricant. And we have added -- and we have used only hydrophilic matrix of sodium CMC.

"Question: All right. So set aside the issue of whether it's a matrix or not.

"The magnesium stearate that's in those compacted granules after that first step is hydrophobic; correct?

"Answer: Yes.

"Question: And then outside of that, you have all these hydrophilic materials that form your matrix; correct?

"Answer: Yes.

MR. LIEF: Okay. I would like to mark as Kulkarni Exhibit 125 a document bearing Bates numbers ZYDUS_MES 347367 through 347402.

"Question: And let me begin by asking you: Have you ever seen this document, Kulkarni Exhibit 125, before?

"Answer: No.

"Question: Okay. Are you familiar with the type of document this is at Zydus?

"Answer: It's an in-process analysis, raw data.

"Question: Okay. When you say 'an in process analysis,' what does that mean, 'in process'?

"Answer: During manufacturing of a batch, this analysis is being done, is done.

"Question: Okay. And so if you look at the

first page of Kulkarni Exhibit 125, which is ZYDUS_MES 347367, am I correct that this is an in process analysis that was done during the manufacture of EMM196?

"Answer: Yes.

"Question: Okay. If you could turn to page 347373.

"Answer: Yeah.

"Question: And -- and if you need to look at any other pages around it, but can you tell me what is reported on this page?

"Answer: This is dissolution data.

"Question: Okay. And it's dissolution data for EMM196?

"Answer: Yes.

"MR. LIEF: And then if I can mark as Kulkarni Exhibit 126 a document bearing Bates numbers Zydus_MES 350240 through 353502.

"BY MR. LIEF:

"Question: And with respect to Kulkarni Exhibit 126, have you seen this document before?

"Answer: No.

"Question: Okay. Have you seen -- strike that.

"Are you familiar with a what this document is at Zydus, what type of document this is ?

"Answer: Yes.

"Question: And what type of document is this?

"Answer: This, this is analytical lab notebook.

"Question: Looking at page ZYDUS_MES 350397, do you see in the upper right-hand corner there it says, 'batch number,' and then it says '1200-F108'?

"Answer: Yes.

"Question: Okay. And can you confirm for me that the dissolution conditions here on this page 350397 in Kulkarni Exhibit 126, are the same pH 7.2 phosphate buffer, paddle 100 RPM, as those that we saw in Kulkarni Exhibit 125 at page 347370?

"Answer: Yes.

"Question: Okay. And coming back to Kulkarni Exhibit 126, if you look at page ZYDUS_MES 350400 -- do you see that?

"Answer: Yeah.

"Question: Do you see that there are results reported on this page for what appears to be batch F108, for dissolution?

"Answer: I can't read the number. There are -- there are --

"BY MR. LIEF:

"Question: There are data there?

"Answer: Yeah.

"Question: But they're not legible, really?

They're very small?

"Answer: Yeah.

"Question: Okay. Let me -- let me mark as Kulkarni Exhibit 127 a document bearing Bates numbers ZYDUS_MES 0349718 through 0349795.

"BY MR. LIEF:

"Question: And with respect to Kulkarni Exhibit 127, have you seen this document before?

"Answer: Yes.

"Question: You've seen this?

"Answer: Yes.

"Question: Okay. And what is this document?

"Answer: It is a lab notebook for formulation.

"Question: Okay. And it's for various formulations that Zydus tried for its mesalamine delayed release tablets?

"Answer: Yes.

"Question: Okay. And if we go to page, Bates page ZYDUS_MES 349763 --

"Answer: Yeah.

"Question: Am I correct that on this page 349763, there is a formulation set forth for Zydus' mesalamine DR tablet batch No. 1200 F108. Is that correct?

"Answer: Yes.

"Question: In terms of the formulation itself

for F108, is this formulation made in a way where the mesalamine is initially combined with colloidal silicon dioxide and magnesium stearate, and then compacted?

"Answer: No.

"BY MR. LIEF:

"Question: Okay. And so in this formulation, F108, the magnesium stearate is only added at the end, before compression?

"Answer: Yes.

"Question: Okay. Other than that, can you confirm for me that the ingredients in F108 are the same ingredients as in Zydus' final exhibit batch, EMM196?

"And to do that, you may want to look at Kulkarni Exhibit 102, at page ZYDUS_MES 235660.

"Answer: It is same.

"Question: Same ingredients; correct?

"Answer: Yeah.

"Question: And, again, as comparing the ingredients in F108 with the final Zydus exhibit batch, EMM196, am I correct that the amount of each ingredients in each tablet is also the same?

"Answer: Yes. It is same.

"Question: Mr. Kulkarni, I have a few questions here. And bear with me; I haven't had as much time as Mr. Lief to prepare here.

"I'd like to take you back to some testimony about the materials that are used in the compaction step in EMM196.

So if you could pull out the batch manufacturing record, which is 102, if you could please, Mr. Kulkarni -- just so I have a good point of reference -- page to the document -- I'm sorry, page to the page ending in -5660 of Exhibit 102.

"Answer: Yes.

"Question: Does this page reflect the materials that are used in the compaction step of batch EMM196?

"Answer: Yes.

"Question: Is the manufacture -- I'm sorry. Let me take a step back.

"What is the name of the colloidal silicon dioxide used in batch EMM196?

"Answer: An Aerosil-200.

"Question: Is it Aerosil-200 Pharma?

"Answer: Yeah. Aerosil-200 Pharma.

"Mr. Gaertner: What number are we on?

"The Reporter: 128.

"Question: During Mr. Lief's examination, you might recall a point in time when he asked you to agree with him whether or not the materials in the compaction phase have any lipophilic excipients. Do you remember generally

that conversation with Mr. Lief this morning?

"Answer: Yes.

"Question: Now, we just established that one of the materials in the compaction phase is the colloidal silicon dioxide known Aerosil -200 Pharma; is that right?

"Answer: Yes.

"Question: Now, I've just marked as Kulkarni Exhibit 128 materials of -- from the website of Evonik Industries that is the manufacturer of Aerosil. I'd like you to take a moment to review that, please.

"Okay. Yeah. And could you read into the record the title of this information, please?

"Answer: Hydrophilic fumed silica.

"Question: And does this indicate to you, Mr. Kulkarni, that the colloidal silicon dioxide used in the compaction step in batch EDM196 is hydrophilic?

"Answer: Yes.

"Question: So in your view, Mr. Kulkarni, does the compaction step in batch EMM196 include a hydrophilic excipient?

"Answer: Yes."

(End of videotaped deposition.)

MS. FARNAN: Your Honor, at this time, we would move into evidence PTX-205, which was Kulkarni Exhibit 117; PTX-208, which was Kulkarni Exhibit 104; PTX-217, which was

Kulkarni Exhibit 103; PTX-287, which was Kulkarni Exhibit 102; PTX-288, which was Kulkarni Exhibit 127; PTX-294, which was Kulkarni Exhibit 113; PTX-295, which was Kulkarni Exhibit 114; PTX-298, which was Kulkarni Exhibit 118; PTX-299, which was Kulkarni Exhibit 119; PTX-303, which was Kulkarni Exhibit 125; and PTX-304, which was Kulkarni Exhibit 126.

THE COURT: All right. Mr. Gaertner?

MR. GAERTNER: No objections, Your Honor.

THE COURT: All right. They are all admitted without objection. Thank you.

(Above-referenced Exhibits admitted into evidence.)

MS. FARNAN: And, in addition, Your Honor, we had notified Zydus by e-mail, a couple of the exhibits that we've just admitted, PTX-208, PTX-217, PTX-287, PTX-295 and PTX-303 are part of the defendant's ANDA.

And we had notified them at the time we moved a portion of the ANDA in, we were going to move the entire ANDA in, multiple volumes. Your Honor does not have all of it. We will provide them to the Court, but I can read into the record now and move the entire ANDA in at the same time.

MR. GAERTNER: The notice we received was under Federal Rule of Evidence 106, which is that if an adverse party moves an incomplete document in, then the other party

can get up and ask to move the rest of it in. We're not moving that in, so I don't see how Rule of Evidence 106 applies.

MS. FARNAN: Your Honor, I guess we're surprised at an objection, because we did not hear one when we sent our e-mail yesterday. And this is a case that is an artificial act of infringement, the filing of the ANDA. And the ANDA, of course, is evolving over time, but at the end of the day, it's one complete submission to the FDA that it was segmented because it evolves over time. We think it's largely irrelevant.

Again, this is a document we're admitting. We're an adverse party to the ANDA and we're just seeking to have the entire ANDA in the record.

THE COURT: Yes. Well, I will tell you what. We're going to take a break. I will let the two of you actually talk about this. All right? See if you can't come to some reasonable agreement, or at least to the point on the objection and the response so that I can pick it up.

We'll go ahead and take a ten-minute break, be back here at noon, and run it for another half-hour, 45 minutes, and then take our lunch break. All right? Okay. We're in recess.

(Short recess taken.)

(Proceedings resumed after the short recess.)

THE COURT: All right. Thank you. Please be seated.

Your next witness, Mr. Haug?

MR. HAUG: Yes, Your Honor. We're actually going to skip over one deposition video.

If we may continue the discussion on the exhibits that we had just before the break over the lunch break, that may obviate the need for that deposition, depending upon if we can reach agreement.

THE COURT: All right.

MR. HAUG: So I'm answering the question we don't have an answer yet on the meet and confer.

THE COURT: Okay.

MR. HAUG: But we will after lunch.

And the next witness I will let my partner, Mr. Lief, introduce.

THE COURT: All right. Mr. Lief?

MR. LIEF: Good afternoon.

THE COURT: Good afternoon.

MR. LIEF: We're going to play the de bene esse deposition of trial testimony of Dr. Davies, who did some testing in the case, and the testing relates to the issue of the location of mesalamine in the accused product.

As a scheduling issue, I'm told the entire

deposition is about 46 minutes, including the cross questioning, and so --

THE COURT: Let's roll it through. If everybody is fine with that, that will be the last thing you do before the lunch break. Okay?

MR. GAERTNER: Judge, Mike Gaertner. I just want to give you a heads-up.

During the deposition there were some objections raised, and since you weren't there, I don't know how you want to handle them in terms of the scope of the testimony as beyond the report. I want to flag the issue with you. It could be that you just want to address it when the objection comes up and I'm fine with it, but I wanted to let you know that that is going to occur.

THE COURT: Let's actually deal it in context. In other words, if there are objections that you still want to stand on, I will expect you to rise, Mr. Gaertner, or whoever is handling the matter.

As soon as you see him on his feet, then let's have the videotape stop rolling and we can deal with the objection then. Is that all right?

MR. GAERTNER: Yes. My colleague, Andrea Wayda, will be doing that.

THE COURT: That's fine.

MR. LIEF: Your Honor, if I might approach, I

don't know how many copies?

THE COURT: One for the clerk, if I might, one for me, and one for the record.

(Deposition binders handed to the Court.)

(The videotaped deposition of Martyn Christopher Davies was played as follows.)

"Question: Would you state your full name for the record.

"Answer: My name is Martyn Christopher Davies.

"Question: And what is your profession?

"Answer: I'm a university professor at the University of Nottingham in the U.K. I'm also, I started a pharmaceutical company called Molecular Profiles, now called Juniper Pharma."

THE COURT: Can we stop just a second here? Am I going to look in vein for highlighting? Is this one highlighted? No, yes?

MR. LIEF: I think this is the entirety of the transcript.

THE COURT: This is the whole thing all the way through. Okay. Got it. Thanks.

"Question: I would like you to look in your book at Plaintiffs' Trial Exhibit 520. Can you tell us what this document is?

"Answer: This document is my curriculum vitae.

"Question: And is the information reported in that document accurate and up to date?

"Answer: I believe it is. There may be one or two publications coming up this month, but I believe it's up to date.

"Question: And --

"MR. LIEF: We would move Plaintiffs' Trial Exhibit 520 into evidence, and as I understand it it's without objection.

"DR. WAYDA: No objection.

"Question: Can you tell us, what is the focus of your work in the pharmaceutical sciences?

"Answer: The focus of my work is in the development and characterization of pharmaceutical dosage forms.

"Question: And how long have you been involved in the characterization or analysis of pharmaceutical dosage forms?

"Answer: I've been involved since my undergraduate days through to my post-graduate days in my academic and industrial career, that must be over 30 years that I've been involved in characterization and testing of pharmaceutical dosage forms.

"Question: If we could turn to Plaintiffs' Demonstrative Exhibit No. 2.1. Can you tell me what this

is?

"Answer: This is a summary of my curriculum vitae.

"Question: And could you point out for us some of the highlights listed here?

"Answer: Yes. I graduated as a pharmacist top of my class. I did my Ph.D. in the School of Pharmacy at the University of London. I am a university professor. I've published over 400 scientific publications. I've trained over 100 post doctor, post-graduate staff, around about 20 of whom have gone on to full academic posts, many have gone into industry.

I founded a company called Molecular Profiles, which is now known as Juniper Pharma, and we won two Queen's Awards for industry in category of enterprise. That's the top category, top award for industry in the U.K.

"I've had a number of awards. I've been made fellow in a number of learned societies, including the Royal Society of Chemistry. I've been president of the Controlled Release Society, which is the premier society of drug delivery, internationally.

"I've also -- our school and the laboratory at our school was given the Queen's Award for industry in collaboration with Molecular Profiles in recognition of the work in translating, our work through the industry.

"Question: Dr. Davies, have you been accepted as an expert in the field of pharmaceutical science and formulation in other Federal Courts?

"Answer: Yes, I have.

"Question: And could you briefly tell us some of those.

"Answer: For instance, I gave evidence in a trial related to the drug called omeprazole. I gave evidence where I did testing using a range of analytical techniques to address specific issues, both included infrared spectroscopy, those included imaging techniques, to determine the structure of formulations.

"I also undertook -- for example, another case I did was related to Exelon (phonetic), and again, in that case I did testing to show the distribution of the drug through the product, and I used Raman spectroscopy and mapping for that.

"Mr. Lief: We would move the Court that Mr. Davies be admitted as an expert in the fields of pharmaceutical science and in the analysis and characterization of pharmaceutical drug formulations.

"Ms. Wayda: No objection."

THE COURT: Okay. Go ahead.

"Question: Dr. Davies, what were you asked to do in this case?

"Answer: I was asked to look at, specifically I was asked to look at the distribution of the drug mesalamine through the Zydus ANDA product.

"Question: And have you done that?

"Answer: I have.

"Question: And what is your conclusion?

"Answer: My conclusion is that the drug mesalamine is distributed homogenously throughout the Zydus product.

"Question: And what is that opinion based upon?

"Answer: It's based on the testing that I undertook. Testing, my analytical testing where I looked at the Zydus ANDA formulation.

"Question: And what samples of the Zydus product did you test?

"Answer: I tested two different batches of the Zydus ANDA product. I tested the EMM196 and I also tested EMM345, which were the -- I believe the 196, which I referred to as the 196 batch, the batch produced most recently, under the most recent manufacturing conditions. That's what I've been advised by counsel.

"Question: And what types of testing did you perform on those products?

"Answer: I performed two specific tests. I performed testing using Raman spectroscopy. I also used

optical microscopy in my analysis of the product.

"Question: Who developed the analytical procedure for the testing of the Zydus ANDA product?

"Answer: I did. I designed the experiments, and the experiments were undertaken by technicians at my company, Juniper Pharma. I took that work, reviewed the data and came to my conclusions.

"Question: If we could turn to Plaintiffs' Trial Exhibit 523, can you tell us what is this document?

"Answer: This document is the laboratory notebook from Juniper Pharma highlighting the experiments that we undertook.

"Question: Is Plaintiffs' Trial Exhibit 523 an accurate and complete copy of the lab notebook?

"Answer: Yes, it is.

"Question: And is this the type of document you would keep at Juniper Pharma in the ordinary course of business?

"Answer: It is indeed.

"Mr. Lief: We would move Plaintiffs' Trial Exhibit 523 into evidence.

"Dr. Wayda: No objection."

THE COURT: It is admitted.

(PTX-523 was admitted into evidence.)

"Question: Turning to Exhibit 2.2, can you tell

us what is shown here?

"Answer: Yes, this is a demonstrative I prepared which explains the experimental procedures that I undertook.

"Question: And can you briefly describe for us those procedures?

"Answer: Yes. So starting from the left, the first, the Zydus tablet was cut using a razor blade, and then we used an microtome with a diamond blade to precisely cut the surface such that we produced a smooth, clean surface suitable for imaging.

"We then undertook optical images using an optical microscope, and we also undertook, which provides a light microscopy of the surface of the cross-section. And on that same cross-section, we then undertook images using a Raman microscope, which provides a chemical image of the surface.

"Question: With respect to the microtoming procedure, is that a procedure that you performed before?

"Answer: It is a procedure performed routinely day in and day out at Juniper Pharma. We've done that for, gosh, and in the academic environment, we must have done that for 20 years. It's a routine approach.

"Question: If we turn --

"Answer: That's how we can look at the internal structure and chemistry of formulations.

"Question: If we could turn to PDX-2.3, can you tell us what is shown in that demonstrative?

"Answer: Yes. This is just illustrating the experiments that I undertook with the optical microscopy. And on the left-hand side we have a general microscope, which shows the tablet on the sample stage, shows an eyepiece through which I can look through, there's the lens just above the tablet, and there's a camera above which allows the recording of the images that we see.

"So in the optical microscope, the light coming from the surface of the tablet is collected through the lens, and then it's captured with a camera, digitally, and that is shown on a computer as is shown here.

"We did that at times one, times two, times three magnification, under the Nikon microscope, and times 20 with a Olympus microscope.

"Question: If we look at Plaintiffs' Trial Exhibit 524, and this is a six-page document. Can you tell us first what is shown on the first three pages?

"Answer: Yes. These first three pages relate to the optical images taken at times one, times two, and times three for the 196 batch.

"Question: And what is shown on the last three

pages of PTX-524?

"Answer: Those are the corresponding images for the times one, times two, times three for the 345 batch.

"Mr. Lief: We would move Plaintiffs' Trial Exhibit 524 into evidence.

"Ms. Wayda: No objection.

THE COURT: It's admitted.

(PTX-524 was admitted into evidence.)

"Question: If we could turn to Plaintiffs' Trial Exhibit 536, again, this is a six-page document.

"I would like to ask you first, with respect to PTX-536, what is shown on the last three pages?

"Answer: The last three pages are the times, again, times one, times two, times three images taken of the 196 batch.

"Question: And then with respect to PTX-536, what is shown on the first three pages?

"Answer: These were the corresponding images of times one, times two, times three of the 345 batch.

"Mr. Lief: We would move into evidence plaintiffs' trial Exhibit 536.

"Ms. Wayda: No objection.

"Except if you could take what the different is between these two exhibits, 526 or -- 524 and 536?

"Mr. Lief: I don't know that we need to. Would we condition an objection if we don't?

"Ms. Wayda: No, no objection.

"Question: Can you briefly describe for us what Raman spectroscopy is?

"Answer: Yes, I have demonstratives that show that.

"Question: Why don't we take a look at Plaintiffs' Demonstrative Exhibit 2.4. And what is shown here?

"Answer: Again, here we have, on the left-hand side of the image we show a general Raman microscope. There is a laser light shown. There is also an eyepiece. There is also an optical fiber which collects scattered light, and you see the top is placed on the sample stage.

"So in a Raman analysis, and Raman is widely used in the pharmaceutical industry as a technique to chemically characterize drugs and excipients. It provides a chemical fingerprint which is unique for a particular drug or excipient.

"And in the experiment, as is shown, you if you have a -- if you have a monochromatic light, which hits the surface, and then you have light which is scattered off that surface. And it's that scattered light that's collected by the eyepiece and analyzed in the spectrometer; and as shown

on the right-hand side, you produce the spectrum. This is just an ideal spectrum which is being shown.

"With the microscope, you can focus to a particular point, and that's shown in the red dot here. And that spectrum is shown with a -- provides a spectrum which is a unique fingerprint, and the position of the peaks within the spectrum are diagnostic of the chemical structure and the bonds that exist within the molecule.

"Now, with a Raman microscope, one can move that point across a sample and take images -- sorry -- take spectra at the points across the sample. One can then say, look for a unique peak for a particular compound, such as a drug, at each point of those red dots, look for that unique piece, and then produce a chemical image, as you see here on the computer screen.

"So it's a chemical analysis technique.

"Question: Have you used Raman analysis before for pharmaceutical products?

"Answer: I've used Raman analysis since the 1990s, and we've used Raman mapping in the pharmaceutical company, and also in our academic work over the last ten years at least.

"Question: If we could turn to Plaintiffs' Trial Exhibit 901, and I will ask you, do you recognize 901?

"Answer: Yes. This is a page from my expert report and it shows Figure 1, which is the Raman spectrum.

"Question: Dr. Davies, we've supplied present counsel with the Plaintiffs' Trial Exhibit 901. Again, could you briefly tell us what this is?

"Answer: Yes. This is a Raman spectrum of the reference drug, mesalamine. So it's just the pure drug. And you see in the horizontal axis, it has the wavelength and the vertical axis counts intensity.

"You see that there is the most dominant peak that occurs around about, towards the middle of the spectra, right about 817, and we used that peak, because that peak is diagnostic of the drug, and we integrated over the region 795 to 835. And we did that in all the Raman spectra that we looked at in a particular region, and we produced the Raman map just of that area, that peak.

"Question: If we could turn to Plaintiffs' Trial Exhibit 902, do you recognize this image?

"Answer: Yes. This is a Raman image taken on a region of 1 millimeter by one millimeter on the cross-section, the same cross-section that we analyzed by optical microscopy.

"Question: And do you know which batch of the Zydus product this comes from?

"Answer: Yes, it's the 196.

"Question: Again, turning to Plaintiffs' Trial Exhibit 903, what is this?

"Answer: This is another area of the same cross-section of the 196 batch, again, one millimeter by one millimeter.

"Question: Turning to Plaintiffs' Trial Exhibit 904. What is this?

"Answer: This is again another Raman image looking for the drug mesalamine, and the same as the 196, but in this case it's the 345 batch. Again, it's a one millimeter by one millimeter, same cross-section that was imaged by optical microscopy.

"Question: And finally, turning to Plaintiffs' Trial Exhibit 905. What is this?

"Answer: Again, it's another image of mesalamine. Another region of the same cross-section of the 345.

"Mr. Lief: And with that, we would move into evidence plaintiffs' Trial Exhibits 901, 902, 903, 904, and 905.

"Ms. Wayda: No objection to PTX-902, 903, 904, 905.

"With that redaction, defendants have no objection to PTX-901."

THE COURT: Admitted.

(Above reference exhibits admitted in record.)

"Question: Looking at the imaging that you produced, does mesalamine exist throughout the picture -- the region that you analyzed?

"Answer: Yes, it does. Mesalamine exists throughout the image.

"Question: And do you see mesalamine throughout the features that you would identify as granules within these pictures?

"Answer: Yes, I do.

"Question: Do you see mesalamine outside of the granular features?

"Answer: Yes, I do.

"Question: Turning to Plaintiffs' Demonstrative Exhibit 2.6. What is shown here?

"Answer: This is an optical image where I've highlighted a black box, the region that I analyzed by Raman. And this is for the 196 batch. This is also an optical image which I annotated regarding the presence of granules and particles.

"Question: Again, what does the black outlined rectangle represent?

"Answer: The black outlined rectangle represents the area analyzed by Raman, by the two maps of the Raman that we undertook within the 196 batch.

"Question: If we turn to Plaintiffs' Demonstrative Exhibit 2.11, what is shown here?

"Answer: Yes. Perhaps if we could just go back to the previous image, I could explain where this comes from. I apologize, the previous image.

"Mr. Lief: To 2.6, please. Not this one.

"Answer: I've highlighted within the black box two regions, G1 and G2, both of which relate to, show the presence of granules. I've highlighted the presence of granules.

"And this next image --

"Question: 2.11.

"Answer: -- shows that region of that first box with, and this is G1. This is the optical image.

"Question: All right. And the circled item with the letter G in it, what is that?

"Answer: That is a region that I've highlighted as a granule.

"Question: Did you find that type of granule throughout the cross-section that you looked at with optical microscopy?

"Answer: Yes.

"Question: If we could look at PDX-2.12. Can you tell us, what is this?

"Answer: This is the Raman image of that same

region that we just looked at by optical microscopy.

"Question: And in this picture, do you find mesalamine throughout?

"Answer: Yes, I do. There is mesalamine throughout.

"Question: Okay. And if we --

"Ms. Wayda: I am going to object to this line of examination and questioning. I believe that Dr. Davies just --

THE COURT: Okay. Do you want to explain your objection, at this point, Ms. Wayda?

MS. WAYDA: Your Honor, we objected to this line of questioning because it was outside the scope of his expert report. If you look back at the granule that has been marked as a G, that granule and that marking was only done at his deposition. That was an exhibit that we created. Within the ambit of his expert report, he never associated a specifically marked granule with the Raman map that he obtained.

If it would help the Court, I can hand you up the expert report and show you why there has never been an association with a specific granule and a specific Raman map. Therefore, it is our contention that this testimony was outside the scope of his expert report.

THE COURT: Okay. Before we get into the expert

report, I'll hear from Mr. Lief, and then I will hear from you again.

MR. LIEF: Your Honor, because we anticipated this issue, we prepared a memo on it. It might help. I can hand that up, but I would obviously summarize the argument.

THE COURT: Hold on to your memo and give me your argument. Okay?

MR. LIEF: All right. Within his expert report, he stated, in what is paragraph 12 of his report, Raman analysis and optical microscopy showed the presence of mesalamine distributed homogenously throughout two representative cross-sections of the Zydus tablets.

That's the Raman.

He also stated in paragraph 20: In my opinion, the particles and/or granules range from approximately 10 micrometers up to approximately 500 micrometers. These features were distributed across the whole of the tablet cross-section.

Now, what these demonstratives do is simply take those two sentences and give you the visual of that.

There is case law on this including case law from Delaware, where testimony, Forest Labs v Ivax, 237 FRD 106, where the testimony is of a nature that either it's, I would suggest it's actually in the report from what I read you, but even where it's a combination of two things that

are in the report, that is permissible. It is an elaboration that is permissible.

THE COURT: Sure. Okay.

Dr. Wayda, do you want to respond?

MS. WAYDA: Yes, I would, Your Honor. Thank you for the opportunity to respond.

Anticipating this action and frankly not being sure how we would preserve the record on this point in the event that there was a continuation of the objection and Shire continuing to say it should come into evidence, in order to preserve the record later in this deposition, during my cross-examination I asked Dr. Davies, who is the best authority on what he had in his expert report, whether or not this image and this particular opinion was actually in that report.

We could wait until we get to it, but I will tell you that on page 43 of the deposition transcript, I asked him:

"Question: But neither in your deposition on February 18th, 2016, nor in your expert report did you associate a specific granule in the optical micrograph with a specific region of a Raman map that is located in your expert report; correct?

"Answer: Again, I am not sure that's correct. I would say that Raman, that specific granule, I would

agree, I didn't say that in my expert report.

THE COURT: Okay. Well, here is what it sounds like to me your opposing counsel is saying. I don't think anybody is saying that in the report, he included that image and said, look, I looked at that specific granule. What I hear them saying is he said in the report, I saw the mesalamine throughout, and I saw it in the granules, and here is a picture of it that in the deposition itself, it is happening. I mean I think I got that from Mr. Lief's comments.

So assume if he were standing here, sitting here on the stand and they threw up a picture there and they said, is this illustrative of what you said in your report? Your objection would be what? We haven't seen this picture before? What would it be?

MS. WAYDA: Your Honor, I think if you recall the testimony, I didn't object when they said it was illustrative. I think they can make that particular combination cobbled together from his expert report.

He simply never identified in his expert report the area of the map of the cross-section where the Raman was obtained, nor did he say that particular granule was associated with that Raman map, and that is what we're objecting to.

THE COURT: So it's that specific image because

he didn't point to that one.

MS. WAYDA: That's right. In fact, I have to tell you in paragraph 20 of his expert report, there are no marked granules. His first deposition, he couldn't mark a granule. It only took the second deposition that he would actually prepare an illustration of what he believed to be a granule so that we could understand what he was talking about in paragraph 20 of his report.

THE COURT: And are you going to be presenting somebody in dispute that there are granules here?

MS. WAYDA: We will present Dr. Gardella in our phase of the case who will dispute that anything can be gathered from those granules other than the fact that there appears to be mesalamine intensity associated with the entirety of the Zydus cross-section.

THE COURT: Well, I'm going to overrule the objection. I am going to go ahead and let the testimony stand. You are going to have a chance to -- you did have a chance to cross-examine while hearing that in greater detail. You will have your own expert on the stand. I think based on the quote I heard from the report, which I don't hear you disputing, this was fairly within what he was describing, even if that specific image wasn't there. So we may have much ado about not much right here, so let's go ahead and move forward.

Is there something else you would like to say?

MS. WAYDA: No, I was going to say thank you for your consideration, Your Honor.

THE COURT: Thanks.

MR. LIEF: Thank you, Your Honor.

THE COURT: Okay. Let's keep rolling.

"Ms. Wayda: (Continuing) He testified that this Raman image relates to the same area that was looked at by optical microscopy. That is outside the scope of his expert report. We will move to strike any testimony like this as outside the scope and under the rule, Federal Rule of Civil Procedure 26(a).

"Question: If we could turn to Plaintiffs' Demonstrative Exhibit 2.13.

"What is this?

"Answer: This is the optical microscope image taken of the second white box that I showed. This is the second granule that I have highlighted, within the region of that black box of the optical image.

"Question: And, again, were those type of granules in your optical microscopy found throughout the cross-section?

"Answer: Yes. Again, this is taken from the 196 batch.

"Question: And if we could turn to PDX-2.14.

What is shown here?

"Answer: Again, this is the same area of the Raman image that relates to the optical image that we see for the granule G2.

"Ms. Wayda: Defendants object, same objection. Outside the scope of the expert report in violation of Federal Rule of Civil Procedure 26(a).

"Question: Within this picture --

THE COURT: Hold it.

"Question: Within this picture, is mesalamine present throughout the picture?

"Answer: It is.

"Question: Do you have an opinion as to whether these images that we've looked at are representative of the entirety of the tablet?

"Answer: I believe they are representative of the entirety of the tablet, and as represented by the optical images that I looked at, I looked at optical images on both the batches, the 196 and the 345. And both showed the same features within those optical images so I believe they are representative.

"Question: Could you summarize for us the opinions you have provided today with respect to the location of mesalamine within the Zydus ANDA tablet?

"Answer: I believe mesalamine is located

throughout the Zydus product. I believe, as my data shows, it is homogenously distributed throughout the product.

"Question: Is that conclusion surprising to you?"

THE COURT: Okay. Your objection?

MS. WAYDA: Yes, Your Honor. I objected again to being outside the scope. Dr. Davies was the Raman spectroscopist and person testifying about optical microscopy. He gave no opinions anywhere in his expert report whether or not what was in the formulation or would result from the formulation was surprising. He goes on to try and give an opinion as a pharmaceutical formulator. That is outside the scope.

THE COURT: Okay. Mr. Lief.

MR. LIEF: Dr. Davies had seen the formulation for Zydus's product, and this last concluding question really plays off an undisputed fact that some 80 plus percent of their product is mesalamine. And, therefore, it's not surprising that it is everywhere. I don't think it's terribly ...

THE COURT: Well, if he didn't opine on it and make a statement about this being a surprising feature, then it is not coming into evidence here now. So that objection is sustained. Go ahead and skip that part of the deposition.

Is that the last question?

MR. LIEF: That was the last question.

THE COURT: Okay. Then we'll go ahead and move to whatever cross-examination there was. All right?

"Question: Is that conclusion surprising to you?

MS. WAYDA: Objection outside the scope.

THE COURT: Skip it.

"Answer: It is, based on, to me as a pharmaceutical formulator ...

"Cross-examination by Dr. Wayda.

"Question: Good morning, Dr. Davies.

"Answer: Good morning.

"Question: On direct, you testified that you used Raman mapping to locate mesalamine in the Zydus ANDA product; is that correct?

"Answer: That's correct. From a chemical viewpoint, that's correct.

"Question: And would you agree with me that Raman spectroscopy is an established analytical technique that may be used to identify the presence and location of chemicals within a pharmaceutical sample?

"Answer: I would agree with that. It can be used for that reason.

"Question: And this would include identifying the presence and location of chemicals other than the active ingredient, in this case mesalamine, within a pharmaceutical

sample; correct?

"Answer: It depends on the context, but I agree, it could be done, but it depends on the context.

"Question: Now, you know that there are other chemicals in the Zydus ANDA product besides mesalamine; correct?

"Answer: There are other excipients, correct.

"Question: And when we're discussing these, would it be all right with you if we refer to these other chemicals as excipients?

"Answer: Correct.

"Question: For example, you understand that magnesium stearate is in the Zydus ANDA product; right?

"Answer: Correct.

"Question: And colloidal silicon dioxide is in the Zydus ANDA product; correct?

"Answer: That's correct.

"Question: And the sodium CMC is in the Zydus ANDA product; correct?

"Answer: That's correct.

"Question: And you also note that sodium starch glycolate hypromellose, also known as HPMC and microcrystalline cellulose are in the Zydus ANDA product; correct?

"Answer: That's correct.

"Question: You weren't asked to determine the presence of and the location of any of these excipients in the Zydus ANDA product; correct?

"Answer: That's correct. I was asked to look at the presence of the drug within the product.

"Question: And so you did not determine if those other materials are present in the Zydus ANDA product in your Raman mapping; right?

"Answer: I mapped for the drugs, specifically, that's correct.

"Question: And you did not see any evidence or the presence of these other excipients in the Zydus ANDA product in your Raman mapping studies; correct?

"Mr. Lief: I'll object to the form, and also as beyond the scope of the direct."

THE COURT: I am just, we're playing it the same waive. If you have an objection you want to stand on here, you have to let me know. Otherwise, this is going to keep rolling.

MR. LIEF: I think the objection here is his entire direct testimony was about the location of mesalamine. There were a few questions about what he didn't do which I guess are okay but then we start to get into a line of questions about, you know, isn't it the case I take it effectively there are no excipients in there or something

like that or you didn't find the evidence of that. I think that is beyond the scope of the direct.

THE COURT: All right.

MS. WAYDA: Your Honor, the entire scope of Dr. Davies' direct was about Raman mapping, and you saw quite a few demonstrative exhibits about the mechanics of how you collect a Raman spectra.

Dr. Davies neglected to tell you how you need to do the analysis in order to be sure that your Raman maps are correct and accurate. And so I was probing whether or not he had done that necessary analysis in order to able to reach a determination that it was only mesalamine that was present in these maps and no interfering peaks associated with the excipients in the Zydus ANDA product.

THE COURT: All right. You know, I think that's legitimately on the edge of going beyond the scope of the direct, but I'm overruling the objection. I will go ahead and hear it.

"Answer: I was not asked to look for the other excipients. I saw -- I saw the impact of the excipients, particularly in terms of the fluorescence, which I relate to in my report.

"Question: Now, before performing the Raman analysis on the cross-sections of the Zydus ANDA product to look for mesalamine, we looked at PTX-901 where you showed a

reference spectrum for mesalamine; correct?

"Answer: That's correct.

"Question: And so you obtained that reference spectrum, PTX-901. What is the purpose of that reference spectrum?

"Answer: The purpose of that spectrum was so that I could be sure that I was looking for the drug itself.

"Question: And is it fair to say --

"Answer: So that I could identify the specific peak, in this case, formulation mesalamine.

"Question: And is it fair to say that you did not obtain a reference spectra for any other chemical in the Zydus ANDA product?

"Answer: I was aware of the other spectra, but I did not obtain specifically for the batches that we used of those excipients, that's correct.

"Question: And you did not look at reference spectra for the other excipients in the Zydus ANDA product in the literature, did you?

"Answer: Not in the literature, because we already knew of the presence, I knew of the presence of the peaks related to the different excipients, because -- because we look at such excipients regularly.

"Question: And I believe in your expert report, and in the previous depositions, when you saw the Raman

spectra that you obtained for the Zydus ANDA product, the only peaks that you saw were peaks assignable to mesalamine; correct?

"Answer: That's correct. When you can look at the individual data, the spectrum of the individual pixels, and the pixels that I saw were of mesalamine.

"Question: And there were no other peaks associated with any other material other than mesalamine, correct?

"Answer: That's correct. Mesalamine is such a strong scatterer, and it's present in the formulation, 90 percent of the formulation. It's a much stronger scatterer than the excipients. In other words, it gives a much more intense spectrum.

"Question: Now, you looked at with Mr. Lief at some PTX exhibits, as well as the demonstratives, at which you looked at granules, and I believe one of those was marked as PTX-906. If you turn in your small book there, we have a similar image. It is DX-44A-318 in your book. PTX-906, if the operator can bring that up on the screen.

Excuse me. That's the wrong image. I believe it's PTX-1006 -- no, PTX-906. I think this was marked previously. Okay.

If you turn with me then, and look at DX-44A-318. I believe you marked this at deposition and identified various granules and particles. Do you remember

this exhibit?

"Answer: I'm sorry, I'm lost now. Which exhibit?

"Question: It's DX-44A-318.

"Answer: Yes.

"Question: Do you have that?

"Answer: I do. Sorry.

THE COURT: Let me stop you there.

(Videotape stopped.)

THE COURT: Is the thing that's shown on the screen, the image that's shown on the screen that's marked PTX-906, is that the same defense exhibit that he's looking at, too? In other words, am I looking at what he's looking at as he's testifying right now?

MS. WAYDA: Yes Your Honor. We resolved this off the record. PTX-906 is the same as DX-44A-318, which is also the same as DTX-1006.

THE COURT: All right. So for my purposes, I'm looking go at PTX-906. It is what he's looking at. That's all I need to know.

Thank you very much. Start it again.

"Question: You identified particles by marking a 'P' outside of the particle; correct?

"Answer: I did.

"Question: And you identified granules by

circling them and marking a 'G' inside; is that correct?

"Answer: That's correct.

"Question: Now, your optical microscopy alone doesn't tell you what's in these granules or particles, correct?

"Answer: That's correct. The optical microscopy tells you when you look at the cross-sections, that there are different -- as I say in my report, different features, granules or particles. You would know as a formulator the different components that are present within the formulation.

"Question: Turn now in your book to DX-44A-317.

"I would ask you the same questions here. I believe there were small dots with a 'P' by them, are that which you identified as particles in this exhibit?

"Answer: That's correct.

"Question: And these circled areas where you've identified granules, are those what you identified as granules in this exhibit?

"Answer: Those are some of the granules that I see, yes.

"Question: And as I believe you just testified, you created both of these exhibits at your February 18, 2016 deposition, correct?

"Answer: I believe that's correct.

"Dr. Wayda: I'm going to mark and move into

evidence as DTX-1006 the exhibit marked DX-44A-318, and mark as DTX-1007 the deposition exhibit identified as DX-44A-317.

"Mr. Lief: No objection.

THE COURT: They're admitted.

(DX-48-318 and DX-44A-317 were admitted into evidence.)

"Question: Now, optical microscopy doesn't tell you where the excipients are described or distributed in the cross-section of the Zydus ANDA product, correct?

"Answer: Well, in terms of the chemistry, the location that would be undertaken by Raman, optical microscopy which we routinely use, shows you the different structures and features that one sees in a cross-section, as you would expect as such a process of manufacture.

"Question: But I believe you just testified even in your Raman microscopy or spectroscopy, you did not see or look for any evidence of the excipients in the Zydus ANDA product, correct?

"Mr. Lief: Objection. Form. Compound and mischaracterizes.

"Answer: I don't believe I said that. I think I said that I was asked to look for mesalamine and I focused on that. And I also saw evidence of the presence of excipients, particularly those which have a high

fluorescence, which tend to mask the Raman signal.

"I also looked at the individual spectrum for the data, and it's dominated by mesalamine -- it is such a strong scatter."

THE COURT: I hope I've made the record clear already, but I'm going to make it clear now.

If nobody rises, I'm taking the objection as waived, so if the tape rolls and there's no further commentary here in the courtroom, whatever objection was stated in the deposition is waived and it's not going to be relied on further. Okay?

Go ahead. Keep rolling.

"Question: But I believe you testified earlier that you did not see any other peaks in the Raman spectra for the Zydus ANDA product, apart from those associated with mesalamine, correct?

"Answer: No peaks that we could attribute, that's correct. It's dominated -- the drug, which is already strongest, gives the strongest signal is present in 90 percent of the tablet formulation before the coating is put on, and it gives a much stronger signal than the other excipients, and it is distributed throughout that region that we examined.

"Question: So with either Raman spectroscopy or optical microscopy, are you able to identify where the

excipients are located in the Zydus ANDA product, correct?

"Answer: Again, I wasn't asked to do that. I was asked to look at the presence of the drug, and show where the drug was within that product.

"Question: Sir, you're not offering an opinion as to where the excipients are located in the Zydus ANDA product, correct?

"Answer: I'm just -- I'm not offering that opinion. I'm offering an opinion related to the presence of the drug.

"Question: So you testified that the granules contain mesalamine, but you did not determine and you are not offering an opinion on whether or not the granules contain magnesium stearate; correct?

"Answer: Again, I've not been asked to give an opinion on that.

"Question: And would your answer be the same if I asked you with respect to the colloidal silicon dioxide?

"Answer: Again, I've not been asked to give an opinion on that.

"Question: Would your answer be the same with respect to sodium CMC?

"Answer: Again, I've not been asked to give an opinion on that. I've been asked to show where the drug is, and I've demonstrated that.

"Question: And to shorten this up, would your answer be the same for the other excipients in the Zydus ANDA product, hypromellose, microcrystalline cellulose and sodium starch glycolate?

"Answer: They would. I've been asked to show the presence of the drug throughout the formulation, is it present throughout the formulation. And I've done that.

"Question: And I asked you those questions with respect to the granules. Would your answers be the same if I asked you the same questions regarding the excipients, not mesalamine, but the excipients with respect to the particles in the Zydus ANDA product?

"Answer: Well, it depends on what you mean by that. The structures that I see in the same regions that I imaged by Raman, all those structures which contain the drug and excipients show the presence of the drug throughout those structures.

"Question: But you did not find any evidence for any of the excipients in the Zydus ANDA product in any of the particles in the Zydus ANDA product, correct?

"Mr. Lief: Objection to the form, and objection, mischaracterizes.

"Answer: Again, I -- you clearly see the presence of the different structures in the optical microscopy, if I understand you correctly, which are

produced by the manufacturing method, where we know the drug and excipients, the same features that we see on the optical microscopy I show contain the drug, whether they be the granule or the regions around that granule.

"Question: Now, and the only thing that you could say is located within the Zydus ANDA product is mesalamine based on your Raman mapping, correct?

"Mr. Lief: Objection, form, mischaracterizes.

"Answer: Again, that's what I was asked to look for is the drug, is distributed clearly from the optical microscopy. There are different structures and features that are present in the formulation, which would you expect. By the way, it's a pharmaceutical formulation. You would expect it to show those features.

"Question: Now, in the exhibits that we marked and have been entered into evidence as DTX-1006 and 1007, and you can look at them in your book if you'd like, marked granules and particles.

"Do you have any evidence or were you asked to look at the chemical composition of the materials outside of those granules and outside of those particles?

"Answer: Well, in the context of the same regions that I -- as I showed in my demonstratives, those regions that I marked as granules contain drug, but the regions outside that I marked as granules contained the

drug. That's what I was asked to look at, to look at the distribution of the drug in the Zydus formulation, and that's what I've done.

"Question: And you were not asked to look at, and I believe you did not detect, any evidence for any of the excipients in the Zydus ANDA product, namely, magnesium stearate, colloidal silicon dioxide, sodium CMC, hypromellose, microcrystalline cellulose, and sodium starch glycolate, correct?

"Answer: I was asked to look at the distribution of the drug throughout the Zydus ANDA product, and that's what I did. I focused on the drug.

"Question: And you did not focus on the excipients, correct?

"Answer: I did not, because I was asked to look at the drug. The drug was present in 90 percent of the tablet formulation. It's also the strongest scatterer.

"Question: And in your Raman spectra that you obtained on the Zydus ANDA product, you found no evidence of any other peaks associated with anything other than mesalamine, correct?

"Mr. Lief: Objection, mischaracterizes.

"Answer: Again, I don't think that's quite correct. I certainly found evidence of the, as I showed, the presence of the other excipients due to the impact of

fluorescence within the spectrum.

"Question: Are any of the excipients in the Zydus ANDA product fluorescing agents?

"Answer: Again, experience indicates with regard to Raman, particularly in pharmaceutical formulations, in the processing itself, can have an impact on the compound and it can cause fluorescence, and fluorescence, particularly for excipients can be, it is, can be detected.

"Question: But the fluorescence that you indicate that you detected, you did not associate that with any particular excipient in the Zydus ANDA product, correct?

"Answer: That's correct, because the fluorescence is so strong.

"Question: And I believe you testified on direct that the G1 and G2 optical microscopy granules that you looked at could be associated with a similar or same region on the Raman map; is that a fair characterization of your testimony?

"Answer: That's correct. It was the same region of the Raman that we showed the presence of the -- that's correct.

"Question: Now, we have an objection to that line of testimony, but in order to preserve your testimony on the record, I'm going to go forward and ask you a few

questions.

"You did not identify any specific particles or granules in your optical micrographs in your actual expert report, correct?

"Answer: That's correct. Because I thought it was self-evident from the optical images that I was observing.

"Question: But you did not mark anything like DTX-1006 and DTX-1007 and include it in your expert report, did you?

"Answer: That's correct, I didn't for the reasons I believe are self-evident.

"Question: And you did not correlate, as you tried to do in your direct testimony today, any features, particles or granules with any of the Raman maps in your actual expert report, correct?

"Answer: I'm not sure that's correct. I certainly talked about the fact that the Raman, where I took the Raman maps, were reflected to be typical or representative cross-sections based on the optical images, and that would be based on my analysis of the optical image of that region.

"Question: But in your direct testimony I heard you say that the G1 granule was associated with the same Raman map that was shown in a previous demonstrative.

That's not the same as representative, correct?

"Answer: Oh, I don't know that. Clearly, I marked that at my deposition, but the features that I saw in the optical image of that region where I took Raman analysis, I believe were representative of the entire tablet.

"Question: But neither in your deposition on February 18, 2016, nor in your expert report did you associate a specific granule in the optical micrograph with a specific region of a Raman map that's located in your expert report, correct?

"Answer: Again, I'm not sure that's correct. I would say that Raman -- that specific granule, I would agree, I didn't say that in my expert report. But I do say that the Raman map showed that the mesalamine is distributed throughout, that is to say that the regions that I looked at by Raman and the optical microscopy were representative of the entire tablet, representative in the context in which I described that the granules and particles are distributed throughout the entire tablet.

"Question: Now, you're not offering an opinion in this case that any of the testing that you've done shows an inner lipophilic matrix in the Zydus ANDA product; correct?

"Mr. Lief: Objection, beyond the scope of the

direct. Objection, beyond the scope of the direct.

"Answer: I've not been asked to give that opinion.

"Question: And, similarly, you're not offering an opinion that any of your testing shows an outer hydrophilic matrix in the Zydus ANDA product, correct?

"Answer: I'm not offering an opinion on that.

"Ms. Wayda: No further questions. Thank you, Dr. Davies.

"The Witness: Thank you.

"Mr. Lief: Plaintiffs have no questions on redirect of Dr. Davies."

(End of videotaped deposition.)

THE COURT: All right. Thanks very much. We will take an hour for lunch. See you back here at 2:00 o'clock.

(Luncheon recess taken.)

* * *

Afternoon Proceedings, 2:00 p.m.

THE COURT: Good afternoon. Thanks. Please be seated.

Let's go ahead and get started. What do we have teed up for the afternoon, Mr. Haug?

MR. HAUG: Okay. The first thing, Your Honor, is we were able to reach agreement on admissibility on some

exhibits that we otherwise would have played a deposition to --

THE COURT: All right.

MR. HAUG: -- to lay a foundation for, et cetera. So I'd like to list those exhibits if I may, Your Honor. They are all, almost all from the ANDA. They're portions of, sections of the ANDA, of the Zydus ANDA.

So that would be PTX-93, PTX-97, PTX-98, PTX-130, PTX-142, PTX-143, PTX-144, PTX-145, PTX-167, PTX-169, and PTX-170.

THE COURT: Mr. Gaertner.

MR. HAUG: So we offer those, Your Honor.

MR. GAERTNER: No objection, Your Honor. I think we're in the process, and as I told Mr. Haug, it is my understanding we will stipulate to the admissibility of our ANDA sections. In exchange, they'll stipulate to the admissibility of the NDA so we don't have to have people up here on regulatory documents.

There is one thing -- and we will read the numbers of the NDA in a moment. There is one issue that just came up when I was talking to Mr. Haug, it does trouble me a little bit.

THE COURT: Before you -- let's deal with this piece first.

MR. GAERTNER: Oh, certainly. No objection to that.

THE COURT: No objection to that. All those exhibits are admitted without objection that Mr. Haug just read the numbers of which he just read into the record.

(Above-referenced exhibits admitted in record.)

THE COURT: Okay. Go ahead, Mr. Gaertner.

MR. HAUG: I am sorry. And I believe I just heard Mr. Gaertner say that he is willing to agree that all of the ANDA would come in provided that we were agreeing the NDA would come in.

THE COURT: Well, that solves -- there you go. Good thinking. Let's let both sides submissions to the United States Government come in.

MR. GAERTNER: Yes, they're very small, Your Honor.

A broader issue that was raised, it seems to me it is an issue I raised with the pretrial order, that the plaintiff still seems to be taking the position that they preserve rights to object to authenticity and foundation to certain documents even though those objections are not listed in the pretrial order.

The reason that gives me pause, Judge, is, of course, we have experts who are going to rely on internal documents. They have experts that rely on internal documents. I think the vast majority of them, no objections show up, and I am trying to figure out what that means

because if I need a fact witness to put in a document, and it hasn't been objected to, so I can have an expert talk about it later, for instance, that is a pretty significant change from what I understood you telling us at the pretrial conference which was if there is no objections, it is coming in as long as somebody talks about it.

So I want to flesh that out now because we need to know going forward how we're going to prepare our case.

THE COURT: Well, I am a little surprised we are still talking about this.

Mr. Haug, is there a reason why we're still talking about this?

MR. HAUG: Well, there is a reason. Because Zydus's counsel is raising this as an issue saying that there are no objections to any exhibits if there is a witness that talks about an exhibit, and that was never agreed to. So that is the dispute.

The pretrial order very clearly says, I am reading from paragraph 22: The parties reserve their right to raise all objections to exhibits as set forth in Exhibits 6 and 7, the listing of the trial exhibit does not constitute an admission as to the admissibility of the trial exhibit. It goes on and basically says the Federal Rules of Civil Procedure apply.

And the issue is not going to be -- if they want

to have a Shire document come in, that is fine, or a Zydus document. It can only come up if it's a third party document, a true hearsay document. And we're not agreeing that simply because an expert gets on the stand and says he has a document that is shown from the third party that it's admissible simply because he is talking about it. That is our objection. But I think we're talking about this in the abstract. There is no objection.

THE COURT: We are talking about it in the abstract, and I guess we'll wait and see what happens, but here is the deal. If a party has listed as an exhibit a document, the purpose of this whole pretrial process is to put that stuff on the table and work it out. All right?

So it is a correct statement of the Federal Rules of Evidence that an expert can rely on a document and the reliance on the document does not make the document itself admissible. That is a true statement.

It is also a true statement that if a party lists an exhibit in the pretrial order and there is not some objection listed to it, it is going to -- you know, I'll get into it, I'll go back, I'll read. I'll go back myself and re-read what the local rules say, I'll re-read what the document, the pretrial order itself says, but I tried to be pretty clear, and that is if you know you have got a document, you guys should be working out what are the

objections to it, to the fullest extent you can, before the trial. Okay?

So now we'll wait and see what's happens. Right? I don't think I have added anything to what I said before in a meaningful way, but if it comes to it, I guess we'll be duking it out. Well, was this listed? Wasn't it? Did you list objections but you didn't list that? I guess we'll get into it when we get into it.

MR. GAERTNER: Okay. Thank you, Judge.

THE COURT: Mr. Haug.

MR. HAUG: Shire's next witness will be Professor or Dr. Steven Little.

If I may approach? Oh, I am sorry.

THE COURT: Yes. Go ahead and swear the witness. Thanks.

(Documents passed forward.)

... STEVEN RONALD LITTLE, having been first duly sworn, was examined and testified as follows ...

THE COURT: Thanks. Please be seated.

Yes, you may approach.

THE COURT: You may proceed, Mr. Haug.

MR. HAUG: Thank you, Your Honor.

DIRECT EXAMINATION

BY MR. HAUG:

Q. Dr. Little, you should have one binder with the

exhibits and also a smaller binder with some slides. Do you have that?

A. Yes, I do.

Q. Okay. What is your profession?

A. I am a scientist and professor of chemical engineering.

Q. And please turn to tab PTX-623.

A. (Witness complies.)

Q. And are you familiar with this document?

A. Yes, it is my CV.

Q. Is the information reported in your CV accurate and up-to-date?

A. Yes. With the absence of perhaps a couple of appointments and some period publications, it seems to be a complete copy.

MR. HAUG: We offer PTX-623.

MR. MILLER: No objection, Your Honor.

THE COURT: It is admitted without objection.

(PTX-623 is admitted into evidence.)

MR. HAUG: Thank you.

BY MR. HAUG:

Q. Dr. Little, can you briefly describe your educational background?

A. Sure. I received my Bachelor's in Chemical Engineering from Youngstown State University in the year

2000.

I then went on to receive my Ph.D. in Chemical Engineering in 2005 from MIT.

Q. And what was the subject matter of your Ph.D. thesis?

A. Well, it was controlled release. Specifically, polymer matrices for controlled release. And I focused also on pH sensitive polymers.

Q. And can you also briefly describe your professional experience since obtaining your Ph.D.?

A. Sure. In 2006, I started as an Assistant Professor in the Department of Chemical Engineering at the University of Pittsburgh.

Then in the year 2012, I was promoted to the title of Associate Professor of Chemical Engineering at the University of Pittsburgh.

That year, I also was promoted to the title of Chair of the Department of Chemical Engineering at the University of Pittsburgh.

Then last year, I was promoted to the title of Professor of Chemical Engineering.

And then later on, that year, I was promoted to the title Endowed Professor of Chemical Engineering.

Q. And what positions do you currently hold at the University of Pittsburgh?

A. I am the William Keckler Whiteford Endowed Professor

in the Departments of Chemical Engineering, Bioengineering, Pharmaceutical Sciences, Immunology, Ophthalmology at McGowan Regenerative Medicine at the University of Pittsburgh.

I am also the Director of the Controlled Release and Biomedical Research Laboratories at the University of Pittsburgh.

Q. What are your current responsibilities at the University of Pittsburgh?

A. Well, I teach courses. For instance, I teach a course on controlled release at the University of Pittsburgh. I also teach courses on what is called transport phenomenon knowledge, which is essentially the study of the movement of mass heat and momentum, which all have an underlying similarity in terms of the processes.

An example of that would be the movement of drugs through a polymer matrix.

In addition to teaching, I also am the PI of a laboratory which works on a variety of projects funded by private foundations.

THE COURT: What is a PI?

THE WITNESS: Principal investigator, which essentially means that I am the director of the program.

In addition to that, we work on about $10 million of research over the last handful of years. And

that is some examples.

BY MR. HAUG:

Q. Thank you. Are you involved in any professional activities outside of the university?

A. Yes, I am. I am also the co-founder of a spin-off company from the university called Chrono, Inc., which is custom designed and formulation controlled release products.

Q. Have you authored any publications on the topic of controlled release pharmaceutical formulations?

A. I have. I am an author and coauthor on about 70 publications that are peer reviewed in the field. In addition, a couple of peer reviewed book chapters in the field.

Q. Have you been appointed to any positions related to controlled release?

A. I am. A number of years ago, I was elected as the chair of the drug delivery special interest group, society for biomaterial, which is an international society. In that role, I led and managed the programming on controlled release, continuing education on controlled release in the society.

After that appointment, I was actually elected to the Board of Directors of that society.

Q. Have you served as a reviewer for any journals in the field?

A. Yes, I review for about 50 journals in the field.

Q. Are you a recipient of any awards or honors that come to note or come to mind?

A. Yes, I list these on my CV, but I have approximately 30 awards that I have been given that I am very proud of.

Just to give an example, last year I was named ASCE's what is called the Curtis W. McGraw research winner which is given to one person in every engineering discipline every year.

Q. Have you been accepted by any court as an expert prior to your testimony today?

A. Yes, I have. About three years ago, I was determined to be an expert in the Southern District of Florida in Shire v Watson.

Also, last year in that same case in the Southern District of Florida in controlled release formulation and testing.

Also, I was considered an expert here in the District of Delaware before Judge Sleet in I believe it was Salix v Lupin case. And that was in controlled release formulation and testing.

Then also I believe last year, it was in New Jersey, and it was Supernus v Actavis, and in that case, I was determined to be an expert in the area of pharmaceutical sciences, and that includes pharmaceutical formulation.

MR. HAUG: Shire offers Dr. Little as an expert

witness in the field of controlled release formulation and testing.

MR. MILLER: Your Honor, I have no objection.

THE COURT: All right. Dr. Little is accepted as an expert witness. Go ahead.

BY MR. HAUG:

Q. Dr. Little, have you been asked to provide any opinions in this case?

A. Yes, I was. I was asked in regard to Zydus's ANDA product whether or not it was my opinion that it was a controlled release oral pharmaceutical composition. And if I did observe controlled release behavior, I was asked for my opinion as to what was responsible for that behavior.

Q. Have you formed an opinion as to whether the tablet core of Zydus's product is a controlled release oral pharmaceutical composition?

A. Yes, it's my opinion that it is a controlled release oral pharmaceutical composition.

Q. Have you formed an opinion as to what is responsible for the controlled release exhibited by Zydus's tablet core?

A. Yes. It is my opinion that the controlled release is provided for by two separate matrices, a lipophilic matrix and a hydrophilic matrix.

Q. Please turn to PTX-1 in your binder.

A. (Witness complies.)

Q. Are you familiar with this patent?
A. I am. It's the patent-in-suit, U.S. 6,773,720.
Q. What is the title of the patent?
A. It is mesalazine controlled release oral pharmaceutical compositions.
Q. I guess for the record, and as an expert, I would ask you a question, are the terms "mesalazine" and "mesalamine" synonymous?
A. Yes, they are.
Q. What is the filing date of this patent, if you know?
A. The filing date is June 14th, 1999.
Q. And who are the named inventors?
A. The named inventors are Roberto Villa, Massimo Pedrani, Mauro Ajani and Lorenzo Fossati.

MR. HAUG: We offer PTX-1.

MR. MILLER: I think it is in evidence.

THE COURT: Admitted without objection.

(PTX-1 is admitted into evidence.)

MR. HAUG: Thank you.

BY MR. HAUG:
Q. Now, focusing on the abstract of the patent, which is PTX-1, what is the '720 patent generally directed to?
A. So if you look at the abstract, essentially it's saying that it is directed to a controlled release oral pharmaceutical composition, and it contains the active

ingredient which is 5-amino-salicylic acid. That's the chemical name for the non-proprietary names we were just hearing earlier. So 5-amino-salicylic acid is mesalamine and mesalazine.

And there is two portions to this, A and B here, two main components. There is an inner lipophilic matrix consisting of substances with a melting point below 90 degrees Celsius in which the active ingredient is there. And then you have the outer hydrophilic matrix in B in which the lipophilic matrix is dispersed. And then you can have other excipients.

Q. Dr. Little, do you need any water?

A. I just, I am having a hard time getting this open.

MR. HAUG: Your Honor, may I hand the witness a bottle of water?

THE COURT: Yes, bring up a bottle of water.

While you are wrestling with the bottle of water, let me ask you this, Doctor.

Mesalamine and mesalazine, are those proprietary names? How did we end up with those for 5-amino-salicylic acid?

THE WITNESS: So 5-amino-salicylic acid is I guess it's the name --

THE COURT: Compound.

THE WITNESS: -- you would learn in organic

chemistry, right? So there is a specific naming that you learn, chemistry-wise. The name mesalamine and mesalazine, these are called proprietary names.

So there are different organizations that determine these names. So, for instance, in the United States, I am trying to remember, there is an acronym and that organization determines the name for the United States, and that is mesalamine. And then there is, I think it is the international one, and then the British one or something like that, and that is mesalazine, and they're the same thing. They're just different names.

THE COURT: Good enough. Thanks.

BY MR. HAUG:

Q. Dr. Little, please turn to PTX-1.3. We're still in the patent. And specifically, to column 2, lines 42 to 43.

Can you briefly describe to the Court what is described here?

A. Okay. Sure. So this is in the background of the invention. And there's the two paragraphs here. So there are two things.

The first portion of it is it says that when you are preparing sustained, controlled release dosage forms of this medicament that's active in the gastrointestinal tract, like mesalamine, it's saying that it's important to ensure that you have controlled release from this first phase

following administration. When I say first phase, this is what it means. It says when inert matrices have the maximum release rate inside the logarithmic phrase. So I need to break this down.

First of all, inert matrices here in this particular patent are synonymous if you read the introduction with lipophilic matrices. It also describes in here how these kind of matrices, the type of behavior that they produce, is that you have a lot of release at the beginning. The rate is pretty high. And then what happens is the rate decreases with time and actually decreases exponentially with time. And there's science behind that. But essentially what you are going to have is, you're going to have a lot coming out and then you're going to have a little coming out.

So what this paragraph says is that it's important to slow down that initial high rate phase when you are delivering it to the gastrointestinal tract topically like this.

And then the second part of this, it says, said object has been obtained by the present invention, which also allows to prepare compositions characterized by a high content in active ingredient. And this is also something that's unique. So you've got a material that's delivered directly to the intestinal tract on topically, so you have

to smooth that out. You also have a very high amount of drug, and those things go together.

Q. Please turn now to PTX-1.4, and to column 4. And please explain what is set forth here.

A. Okay. So this is a portion of the patent that lists the examples. And starting here in column 4, it goes through column 5.

What's shown on the screen here is one of these examples, but there are five of these examples, and they represent exemplary -- they're exemplary formulations that represent the invention.

Q. All right. Would you please turn to PTX-1.5 and specifically to where it says claim 1?

Do you see that?

A. Yes, I do.

Q. And without reading the whole claim into the record, can you just at least walk the Court through what is required by this claim?

A. Okay. Sure. So underneath of line 4, which is what is claimed is, you have claim 1. It says, similar to the abstract. It's a controlled release oral pharmaceutical composition and it lists the active. That comprises A, B and C.

So A again, the inner lipophilic matrix. And then it says, consists of substances selecting from the

group consisting of and then there's a list of things. Those things have a melting point below 90 degrees C.

And then the active ingredient is dispersed both in the lipophilic matrix and also in the hydrophilic matrix, which is discussed in B. So B is an outer hydrophilic matrix wherein the lipophilic matrix is dispersed, and that outer hydrophilic matrix consists of compounds selected from the group consisting of and it lists those things.

And then C says you can optionally have other excipients in there. And then underneath of that it says, this is the loading amount. It says, wherein the active ingredient is present in an amount of 80 to 95 percent by weight of the total composition.

And then the last part just says that the active ingredient is dispersed both in the lipophilic matrix and in the hydrophilic matrix.

THE COURT: Let me ask a question. It says an inner lipophilic matrix and an outer hydrophilic matrix. It also says that the hydrophilic matrix is such that the lipophilic matrix is dispersed.

THE WITNESS: Yes.

THE COURT: What does that mean?

THE WITNESS: Okay. So first I want to make sure I understand what you said, because you said there was

an inner lipophilic and outer hydrophilic.

THE COURT: Right. That's what it says there. Right?

THE WITNESS: Yes.

THE COURT: All right. I'm just trying to get you to, from your perspective as an expert, to explain to me what it means to have the lipophilic matrix, which I take to be the inner lipophilic matrix, dispersed --

THE WITNESS: Right --

THE COURT: -- in the outer hydrophilic matrix.

THE WITNESS: I guess sort of a way to visualize that, if you have the lipophilic matrix and that then is going to be in pieces and that's going to be dispersed throughout the hydrophilic matrix. So you're going to have volumes here that are separate from the hydrophilic matrix, but those volumes are dispersed throughout of the hydrophilic matrix.

THE COURT: All right. Go ahead.

MR. HAUG: Certainly.

BY MR. HAUG:

Q. What does claim 3 recite, if you know? If we could just move on.

A. It says that those compositions that we just read are in the form of tablets, capsules, or minitablets.

Q. All right. Thank you.

So I'd now like to focus on your opinion that the Zydus tablet core is controlled release.

Why does your analysis focus on the tablet core of Zydus' product?

A. Well, it's my understanding that the Court has determined in this case that coatings that would be on a formulation are not a part of the controlled release oral pharmaceutical composition, so I focus on what's underneath the coatings of the core.

Q. And what is your understanding of the meaning of controlled release?

A. Well, controlled release is anything that's longer than immediate release. Immediate release has a good definition. For immediate release is about 75 percent total release in 45 minutes.

So if you have more than 75 percent release in 45 minutes, that's immediate release. If you have less than 75 percent, that's lower. So that is controlled release. You can also pick a time point later on. Say two hours, three hours. It could take that long for you to get to 75 percent release. That's controlled release.

Q. What evidence did you consider in forming your opinion that the Zydus tablet core is controlled release?

A. I considered the dissolution data that was provided by Zydus to the FDA, and I also considered dissolution data

on Zydus's ANDA product that was performed by Vivian Gray the Court saw earlier.

Q. Would you please turn to PTX-626?

A. (Witness complies.)

Q. Can you identify this document?

A. This is the letter that was provided. My understanding is this is a letter that was provided by Zydus to the FDA, including dissolution data. If you look down here on the box a little bit lower down, three quarters of the way down, you can see the batch number which is EMM196.

Q. Please turn to PTX-626.11.

A. (Witness complies.)

Q. Generally speaking, what is shown on table 7 on this page, if we can highlight that?

A. Sure. This is the actual dissolution data, and the data is represented by the numbers at the bottom which are percents of what was released. This is for the test product which is in the left-hand column. That test product is batch number EMM196. And on the right, it is for the reference product which in this case is Lialda.

Q. Which data in this table reflects dissolution of the Zydus tablet core?

A. Okay. It's the data that's underneath of evaluation stage. There's also numbers above evaluation stage. They're all zeros, but those are in the pre-treatment

stages, and the Court saw that earlier, that they're put into an acidic solution of the representative pH and then early you test in pH 6.4. Those are all zeros. Once it gets past that point and it gets into the higher pHs, that's when the enteric coating is designed to dissolve away.

So this enteric coating is something that protects it from the stomach until it gets past that, and then you would expect it to dissolve pretty rapidly, and, in fact, that's what you see in Zydus' ANDA product.

Q. Did you prepare a demonstrative -- withdrawn.

Are you aware of Ms. Gray's dissolution studies that she did?

A. Yes, I am.

Q. Have you reviewed that data and the images created?

A. Yes, I have.

Q. And did you prepare a demonstrative with Ms. Gray's images to illustrate what's happening here regarding dissolution?

A. Yes, I have.

Q. If we could go to your slides. I think it will be PDX-4.1.

A. Okay. So this is the slide that I prepared. One was essentially showing a composite of images that go through up to 30 minutes in pH 7.2. But the first two images, this one and this one (indicating), those are in the pre-treatment

stages, so this one is in the acidic stage. This one is in the pH 6.4 stage.

So there's a color coating that's on top of these that are dissolved away in the stomach. That's why you see this one is red and this one is white. But underneath of that color coding is essentially this enteric coat that I'm talking about. It's relatively smooth on the surface.

What you see is when you put it in pH 7.2, which is right here (indicating), not very long after that, you go down to here. You can see that coating is gone, which is exactly what it's designed to do. These pH sensitive polymers are designed that once you get them into a different pH, it almost is like a switch. Just dissolves away by design.

Q. It would be helpful, Dr. Little, in particular if you are using the laser pointer to identify exactly what you are referring to --

A. Of course.

Q. -- because the record won't pick that up.

A. So the first image in the acidic stage is PTX-900.18.

The second image in pH 6.4 is PTX-900.38.

The third image on the top is PTX-900.67. That's in the start. PH 7.2, phosphate buffer.

The bottom after 15 minutes in pH 7.2 phosphate

buffer is PTX-900.85.

In the bottom right is after 30 minutes and pH 7.2 phosphate buffer, and that's PTX-900.108.

Q. Thank you.

Go back to PTX-626. Move to page 12. That would be 626.12.

A. Yes.

Q. Please tell us what is shown here.

A. Sure. This is a little difficult to see here because of the photocopy, but this is essentially a draft, a plot of the data that is only from the evaluation stage down. So this graph does not include zeros. It would be in the pre-treatment stages.

So what you see here in times zero hour, that's the start of when the tablet was placed in pH 7.2 phosphate buffer, which is on your left, and pH 7.5 phosphate buffer, which is on your right.

What you see is on the Y axis here is the percent of drug released, so you would go from 0 to 100, and on the Y, on the X axis, my apologies, X axis on this, the time point, one, two, four, six and eight hours.

And the key, you can see here that there's the Zydus product, and then you can also see that it's Lialda here as well.

Q. Do you know why they're using phosphate buffer?

A. Well, so as the Court heard earlier, phosphate buffer is something that's used in these experiments. It's standard and it represents the conditions later on in the gastrointestinal tract and in the colon.

Q. Did you prepare a demonstrative with regard to this data?

A. I did. The data there was not super clear, so I just replotted it.

Q. What is shown, what are you showing here on your PDX-4.2?

A. Sure. It's the same thing, just replotted with the zero starting here. What you can see is the release starts over essentially a six-hour period. That is when it reaches almost 100 percent, but it definitely is after four hours by that point in time, you're still not, you know, you just get to 70 percent at that point in time.

Q. How, if at all, does this data inform your opinion as to whether Zydus' tablet core is controlled release?

A. This is a controlled release product.

Q. Why?

A. Because the release takes longer than 75 percent in 45 minutes.

Q. Did you consider any other evidence in forming an opinion as to whether the Zydus tablet core is controlled release?

A. Yes. I also considered similar dissolution data that was provided by Vivian Gray, and it also shows that the tablet takes longer than, takes longer than 45 minutes to release 75 percent of the drug.

Q. All right. We'll come back to some of Ms. Gray's data.

First, I would like to ask you about your opinion. What is responsible for the controlled release of the Zydus product?

A. Okay.

Q. What is responsible for it?

A. It's my opinion that what's responsible for this controlled release is two separate matrices, one that's lipophilic and the other one that is hydrophilic.

Q. What evidence did you consider in forming your opinion?

A. Well, I considered the patent specifications, the patent claims. I considered the claim construction. I considered the batch records, which include the composition and the manufacturing process for the ANDA product.

And, in addition to that, I considered not only the images that were provided by Ms. Gray, which shows the time course as the tablet goes through that time course that you are seeing right here, but also the dissolution data itself in terms of how it matches up with what the '720

patent says.

Q. I would like to discuss your opinion that Zydus, the Zydus tablet core contains two separate matrices. So please turn to PTX-1 again, and specifically to column 3, lines 57 to column 4, line 5.

A. Mm-hmm.

Q. And can you describe what's shown here, or explain what's shown here?

A. Sure. So this is the portion of the patent in the disclosure of the invention that talks about what the behavior would be in the system if you had an inner lipophilic matrix that was surrounded by an outer hydrophilic matrix, and it just describes how that system would make it.

And I will just read it. It says, in terms of dissolution characteristics, the compositions of the invention provide a release profile of the active ingredient more homogeneous than the traditional systems. And this is important because this is the point of using two matrices together, so you have more homogeneous than either one of them.

It says, in fact, the immediate penetration of water inside the superficial layer of the hydrophilic matrix and the consequent swelling due to the distension of the polymeric chains of the hydrogels, gives rise to a high

viscosity hydrated front which prevents the further penetration of water, linearly slowing down the dissolution process to a well determined point which is located about half the thickness.

And then it says, until further penetration of water causes disintegration of the hydrophilic layer and therefore the release of the content, consisting of lipophilic granules.

So Your Honor was talking before about being dispersed. So this is what would be dispersed, these lipophilic granules. And as it erodes away, you would see these come out. However, those things then induce the diffusional mechanism typical of those structures, and that further slows down the dissolution profile.

So, again, this describes what would happen, what a tablet would look like if you actually did this. And then it says, essentially, that through both of these together, that you would get a more homogeneous release profile.

Q. And what does the specification mean by more homogeneous?

A. Right. So I created a demonstrative to show this. Yes.

So what I've done here, on the left-hand side is I've included a little excerpt from column 1, which talks

about the release profile that you would get from the individual matrices. And then on the right I've shown what that looks like in terms of a dissolution profile, which is what we've been seeing here.

So I will start with the top, and this is lipophilic matrix. And, again, that's used synonymously in this particular patent with inert matrices. So it says, inert matrices, for example, generally entail nonlinear, but exponential release of the active ingredient.

So on the right-hand side I'm depicting what this would look like. You have a high amount of release at the beginning and then it starts to drop. In fact, it drops mathematically in an exponential matter. It gets exponentially smaller as it goes. Hence, a lot at the beginning, low at the end.

A hydrophilic matrix, on the other hand, is described as having a linear behavior until a certain fraction of the active ingredient has been released. Then they significantly deviate from linear release.

So I'm trying to depict that on the bottom here with this profile (indicating), which would stay straight for awhile, but then it would deviate from that. And remember, we're talking about a pretty high solubility drug. It's 80, 90 percent, 80 to 95 percent in here. So once it gets to the point where, you know, you've got full hydration

and you start to see surface area increase, all of that surface area can contribute more to the dissolution of the drug, so typically what you have happen, you would have it go up.

Q. What would it look like if you were only -- if you only had mesalamine?

A. Well, if you only had mesalamine, it would just be released all at the beginning because there's nothing to keep it from dissolving. As I said, mesalamine is a very highly soluble drug.

Q. So I'd like to ask you now about the claim construction that formed your opinion. All right?

Which claim constructions did you consider in forming had your opinion that the Zydus product contained two separate matrices?

A. All right. So I'm listing them here, the inner lipophilic matrix and outer hydrophilic matrix. My understanding is inner lipophilic matrix is construed to be a matrix that exhibits lipophilic properties and is separate from the outer hydrophilic matrix.

An outer hydrophilic matrix is a matrix that exhibits hydrophilic properties and is separate from the inner lipophilic matrix.

Q. How do these constructions inform your opinion that the Zydus tablet core comprises separate matrices?

A. Well, what I would be doing then, based on these constructions, is I would be looking for two separate matrices. And what I would want to do, I would want to see that they're separate and I would want to see that they exhibit their respective properties.

Q. And how do you know that the matrices in Zydus' tablet are separate?

A. Well, I can see that from the -- well, I can see what I would expect to have happened from the manufacturing process and also the composition. But I can actually see it in the pictures that were provided by Ms. Gray.

Q. All right. Let's turn to Zydus' manufacturing process for a bit.

Please turn to PTX-287. Are you familiar with this document?

A. Yes, I am. This is the batch records for Zydus' ANDA product, and the batch number here is EMM196.

Q. And how did this inform your opinion, if at all, as to whether Zydus' product comprises separate matrices?

A. All right. Well, these batch records include the manufacturing process, and specifically, the compositions of what's in the tablet, and even more specifically, the composition as to what goes into each part of the manufacturing process.

THE COURT: Can you identify what page we're

looking at here?

MR. HAUG: We are turning to -- I think we're looking at page 4.

THE COURT: Page 4?

MR. HAUG: 287. PTX-287, page 4.

BY MR. HAUG:

Q. Once again, what was shown there?

A. All right. So what the Court sees here again, this EMM196 at the top, I think this was actually shown earlier in one of the deposition testimonies. But you can see here the general stages of formulation underneath of bill of material here. So in all caps, "COMPACTION" is listed as a word, and then you see the materials that are added in that compaction stage.

That product as a result of that goes into the granulation stage, which is next, in addition to these materials that are listed here. Then that material in turn goes into the lubrication stage along with these materials.

And then if you actually go to the next page, you can see that those, that final product is -- goes through a functional coating. It lists those materials. And then this film coating that contains this Opadry brown that gets that color that the Court saw earlier.

MR. HAUG: We offer PTX-287.

MR. MILLER: No objection.

THE COURT: All right. Admitted without objection.

(PTX-287 was admitted into evidence.)

BY MR. HAUG:

Q. And before we continue, you earlier testified about PTX-626, which was a Zydus document from the ANDA. We also offer PTX-626.

MR. MILLER: Defendants have no objection.

THE COURT: All right. That, too, is admitted without objection.

MR. HAUG: Thank you.

(PTX-626 was admitted into evidence.)

BY MR. HAUG:

Q. Staying now back on PTX-287, have you prepared a demonstrative to explain this process?

A. Yes, I have.

Q. All right.

A. So what I did here was kind of what I just saw the Court through here with words earlier. I put the materials on the right-hand side that are listed under what the stage is called in the prior chart from the batch record.

So if this is listed out here -- and I will take the Court through this. Most notably, I think this is important, is that you have in this manufacturing, particular manufacturing process, you have two separate

granulation stages.

So what a granulation is, is it's something that is supposed to take the materials, which are usually mixed up before you do it, and stick them together. That is the purpose of the granulation. Okay?

So there are two different types. Not only is there two granulation stages, but there are two different types of granulation. The first one is called a dry granulation, which is what you use this compactor for. That sticks things together because of the malleability of the individual components.

And you press them together with a compaction roller, so the rollers go like this. What happens is each of those things, because of the malleability, they get pressed together and stick because of almost like a zipper, because you press them like that.

So that's where the first stage sticks things together. The second stage is a wet granulation process. You essentially spray on like a polymer glue. It's solubilized first. You spray on water and just like, you know, sand in a sandcastle sticks together because of the water bridges between them that's how you stick those together. It goes through a drying stage that takes the water away, but that's how it sticks.

So if we just start at the top again, I will

show you.

So this -- mesalamine is the active agent. You have colloidal silicon dioxide and you have magnesium stearate. These things are put through rollers and they're stuck together. What comes out of that roller is essentially a flat ribbon that comes out. That goes into an oscillating granulator, and then that oscillating granulator basically breaks that ribbon up into little granules. Those granules go through a sieve, and that sieve I think was about .8 millimeters.

So you would expect the product, those granules to come out of there to be less than .8 millimeters. They wouldn't be exactly .8. They would be like maybe 500 and less than that, okay, that would fall actually through those holes.

Those things then are taken to the next stage, okay? So you have the thing from the first stage and then you have the other things, sodium CMC and sodium starch glycolate. Those are hydrophilic materials. And what is going to happen in the granulation stage is you have purified water and hypromellose which is the polymer I was referring to before. That is sprayed on top of these mixed up ingredients and these hydrophilic ingredients are going to stick to the outside of what came out of that first stage. Okay?

That then gets filtered through a 1.2 millimeter filter, which is bigger, so now you have a bigger mass with little masses inside of it surrounded by hydrophilic material. That is going to be filtered out.

And then you have the final two stages which is the final blending and lubrication where the materials are added here, and then the tableting stage where it is pressed down.

And then if you go down, if you were to continue going, I don't list those here, but those are the coatings.

Q. How did the Zydus process inform your opinion that the Zydus tablet contains two separate matrices?

A. Well, as I described earlier, you actually have in this particular manufacturing process, two separate matrix forming steps essentially. You have the first one where you have the compaction of those materials at the top with the mesalamine, colloidal silicon dioxide, and magnesium stearate, and what is placed around it is the hydrophilic. And so that forms what I expect the formulation to look like.

Q. I would now like to ask you about your opinion that the two matrices in the Zydus tablet exhibiting separate properties. What evidence did you consider in forming that?

A. Right. So besides what I would expect to see from the manufacturing process and the chemicals, I also utilized the images and the dissolution data that was provided by

Vivian Gray.

Q. How did Ms. Gray's images and data inform your opinion?

A. Well, I will take you through it in a minute, but essentially what it shows is that you can actually see the two separate matrices and, more specifically and more convincingly, I think you can see them in pretty much the exact same way that the '720 patent describes. You can see them as I read it earlier.

Q. And I would like you to turn to PTX-900.84.

A. (Witness complies.)

Q. I think you have the slide. It's up on the screen, PDX-4.7. What does this show?

A. This is the -- the first image I am showing is after nine minutes in pH 7.2 phosphate buffer.

You can see here it is about less than five percent release. And what you can see here is underneath of this enteric coat that I showed you before, you can actually see the contents that are underneath of it swelling out and kind of coming out from underneath of it in that part. So that swelling is something that you notice here.

You can also see the tablet edges which were previously very sharp are starting to round out. So what is underneath of that edge is the materials that we saw earlier, and what you see is they're kind of swelling and bulging out to sort of round those edges off.

Q. How do you know that the swelling is attributable to the CMC and SSG in the outer volume?

A. Well, I think that that is what you would expect CMC and SSG to do. They're very well known to be hydrophilic matrix formers. And if you put them in a formulation like this, I think that would be responsible for the swelling.

Q. All right. Please turn to PTX-900.93.

A. So this is after 18 minutes, and pH 7.2 phosphate buffer. And what is released here is about 5 to 15 percent.

And what is most notable in this picture is that you can actually see these granules that we have been talking about here coming out.

And you can, if you look here very carefully, you can see the pits. And I used arrows here, but I will try to use my laser pointer, too. You can see them all over the place here.

So this is not smoothly, dissolving down. You actually see eroding away a little bit of the outer surface. And as that happens, you see the places where the granules used to be and the granules are coming out.

Q. How do you know that the particles in these images are granules?

A. Well, as I described earlier, that first compaction stage densifies those granules, and you have a certain chemical composition that is going to give it a property,

and then around it you have these hydrophilic materials which are swelling up. So if you have that separate properties, what you expect might happen and what I think you are seeing here happen is that what is swelling up around it is pushing and popping these little granules out and that is why you are seeing them there.

Q. Have you formed an opinion as to whether these granules exhibit a separate property from the outer hydrated mass?

A. Yes. As I said, you can see that they would be exhibiting a separate property. Otherwise, you wouldn't see these pits. If they would be exhibiting the same property of what is around them, then you wouldn't see that.

Q. Please turn to PTX-900.239.

A. (Witness complies.)

Q. What does this image show?

A. So what you are seeing here is after two hours, at 11 minutes and pH 7.2 phosphate buffer.

And this image, by this point you released about 70 percent, and this image you see what you saw before. You are still seeing granules come out of this as we go. But most notably by this point, you see it appears as if the tablet is smaller. That is because you are starting to see this hydrophilic stuff eroding away. The layer sort of disintegrates as it goes down, and that is why you are

seeing this.

Q. And please turn now to PTX-900.186.

A. (Witness complies.) So this is a composite image that I created. And I picked three different time points: One hour 29 minutes is PTX-900.186. Two hours and 11 minutes in the middle is PTX-900.239. And on the right, three hours, ten minutes, PTX-900.266.

And the only reason I did this is to show this erosion over time. You see this layer gets, as it goes away it gets smaller and it gets smaller.

Q. The slide you are referring to is PDX-4.10?

A. Yes. 4.10.

Q. Please turn now to PTX-900.281.

A. (Witness complies.)

Q. What is shown in this image?

A. This is after three hours and 40 minutes in pH 7.2 phosphate buffer. At this point, 98 percent has been released, about, and you see it is essentially getting very small at this point, almost none of it left, and you have the final granules in this coming out.

Q. Are all of these images that we have been looking at in the evaluation stage?

A. Yes, they are.

Q. So it's after the enteric coat comes off; is that right?

A. Yes, and that is this time point up above. It's three hours and 40 minutes since it was placed in that buffer stage.

Q. I'd like you to turn to PTX-900.285.

A. This is after four hours in pH 7.2 phosphate buffer. And at this point, approximately 100 percent has been released, and you see the tablet has pretty much fully disintegrated.

Q. That's on slide PDX-4.12; right?

A. Yes.

Q. Dr. Little, we have just gone through a selection of Ms. Gray's images. How, if at all, do these images relate to the patent's description of separate matrices?

A. Yes, I created a demonstrative to show you this.

I'll start in this top column. And I have listed three images: PTX-900.68, which is the first one; PTX-900.78, which is the middle one; and PTX-900.82, which is the one on the right. And with those, I'll just read what I read before.

It says: Immediate penetration of water inside the superficial layer of the hydrophilic matrix and the subsequent swelling, which is what I see in the pictures.

If you go to the next column, or row -- I am sorry -- down, I have two images. On the left, PTX-900.85 and PTX-900.180. And those are representative at least of

what I was saying before, which is the further penetration of water causes the disintegration of the hydrophilic layer.

And, therefore, if you go to the next one. I'll read the PTX numbers in a second.

What it says what will happen as a result of the erosion is the release of the content which consists of lipophilic granules would then go into that particular part that it is supposed to do.

And we saw that throughout up here, but you see it here, and we see it here. As it erodes down, the granules come out.

And the first image is PTX-900.186, PTX-9030.239, and PTX-900.266.

Q. Please turn now to PTX-900.1053.

A. (Witness complies.)

Q. Are you familiar with this data?

A. Yes. This is the dissolution data that was provided by Ms. Gray in a similar format that the Court has seen here. There is percent mesalamine dissolved on the Y axis and hours on the X.

Here, though, you are seeing the pretreatment stages of 0, right here. So the time point in which the evaluation stage begins is at three hours, and it goes to seven.

THE COURT: What exactly is the pretreatment

stage for that?

THE WITNESS: Yes, that is a good question. So when these are analyzed, what happens is essentially to, usually the goal of this is to prove that the enteric coating doesn't come off in the more acidic stages like it is designed to not come off. So you don't see any release in these pretreatment stages. And by that, I mean the more acidic media that represents the pH of the stomach and the early intestine. Okay? So that is the .1 molar normal HCL and the pH 6.4 phosphate buffer.

At three hours, what has happened is that the tablet is placed into pH 7.2 or 7.4 phosphate buffer. That represents the conditions under which that enteric coat will go away; and what you are seeing then is the release behavior from the underlying core.

THE COURT: All right. Thank you.

BY MR. HAUG:

Q. Were you finished with the data shown on this slide?

A. Yes. I was going to add that because the core releases over this three to seven hours, I've, in the next slide, just shown that, to just show release from the core.

Essentially, what you are seeing here is that you -- I'll say that you don't see. You don't see this bursting behavior or this high rate of release that logarithmically decreases, which is what you would expect to see if you only

have a lipophilic matrix. And what you also don't see is you also don't see some amount of steady release until you get to the point where it increases or even decreases.

What you see is you see this steady throughout the entire course. And from release data overall, this is a very, very steady homogenous release profile.

Q. Now, you mentioned earlier I believe that the patent describes a significant deviation from linear release. Do you recall that?

A. Yes.

Q. When only a hydrophilic matrix is used; is that correct?

A. Yes.

Q. Does Ms. Gray's dissolution data show this type of deviation?

A. No, it doesn't.

Q. How did Ms. Gray's dissolution data inform your opinion there are two separate matrices in Zydus's tablet?

A. As I described, what you are seeing here is consistent with two matrices that are working together to provide something that is more homogenous than if you had just either one of the two. And that is entirely consistent with both the pictures that show two separate matrices very clearly, and it also is consistent with the manufacturing process, which would show what I would expect to see which

is manufacturing two separate regions that would exhibit separate properties.

Q. And so what is your overall conclusion about the release profile of Zydus's ANDA product?

A. That it is entirely consistent with my opinion that what is responsible for the controlled release behavior is two separate matrices, one lipophilic and one hydrophilic.

MR. HAUG: Thank you. No further questions.

THE COURT: Cross-examination.

MR. MILLER: Your Honor, may I approach the bench?

THE COURT: You may.

(Binders passed forward.)

MR. MILLER: Your Honor, may I approach the witness?

THE COURT: You may freely approach the witness. Thank you.

(Binder passed forward.)

CROSS-EXAMINATION

BY MR. MILLER:

Q. Good afternoon, Dr. Little.

A. Good afternoon.

Q. It's good to see you again.

A. Good to see you.

Q. It's your opinion that magnesium stearate and

colloidal silicon dioxide impart a lipophilic nature to Zydus's roll-compacted mesalamine and make up what you believe is the inner lipophilic matrix; correct?

A. What I can say from my observations, that I see an inner lipophilic matrix. I see that behavior and it plays out in the release profile. I think it's my opinion that the magnesium stearate is imparting the lipophilic properties, but it's the overall, the overall behavior that I see that informs my opinion.

Q. You submitted an expert report in this case; correct?

A. Yes.

Q. Could we go to that? That is Tab 4 in your binder. And I would ask you to turn to page 28, at paragraph 56.

It reads: I agree with Dr. Hoag's conclusion that magnesium stearate and colloidal silicon dioxide impart a lipophilic nature to Zydus's roll-compacted mesalamine and make up the inner lipophilic matrix.

Did I read that correctly?

A. Yes, you did. What I am trying to say here is this overall material behavior because it is everything that would be in here.

Q. It is your opinion that any resistance to water exhibited by the so-called inner volume in Zydus's ANDA product is due to the addition of magnesium stearate and colloidal silicon dioxide; correct?

A. Well, I think you see resistance to the penetration of water is what I am saying here.

And what specifically -- what I will say specifically is responsible for that is most likely, and I think probably more than most likely, the magnesium stearate, but what I can tell is just from the overall material, so it is everything that is there, which is why I list both of them.

Q. You recall being deposed in this case; correct?

A. Yes.

Q. And you recall that I was present?

A. You were present, yes.

Q. And a stenographer was present as well?

A. I am sorry?

Q. A stenographer was present as well?

A. Yes.

Q. And you were under oath?

A. Yes.

Q. Could you turn to your deposition transcript which is Tab 5 in your binder?

A. Um-hmm.

Q. And I would ask you, if you would, to go to page 166.

A. (Witness complies.)

Q. At line 14, I asked:

"Question: Does the colloidal silicon dioxide

that Zydus uses in its product oppose or resist the penetration of water?"

And you answered:

"Answer: Well, what I can say is that the combination of magnesium stearate and colloidal silicon dioxide with the mesalamine does. I can say that definitely."

Did I read that correctly?

A. Yes, and I say that definitely because what I am saying is that is the overall material that I see that has the effect. And I think we were having a conversation about this at the deposition as to what is responsible. I can say definitely that it is the overall material that exhibits the effect.

Q. Let's, while we're on your deposition transcript, tab 5, let's go to page 179, at line 11. I asked:

"Question: And do you know what's causing in your opinion the resistance to water in the blended mesalamine?"

And you answered:

"Answer: Well, it certainly has something to do with the composition because in the one case, there is not all the ingredients and the other one there is, so the combination of those excipients imparts in some way, shape and form this resistance to water. I can say that.

I asked you:

"Question: Do you know whether or not the colloidal silicon dioxide in the blended compacts is causing resistance to water?"

And you answered:

"Answer: It may not be imparting resistance. It may. I can tell you that the whole thing together is imparting resistance."

And I asked:

"Question: But if I asked you correctly, you are not sure what it is that is causing that resistance?"

And after your counsel objects, you answer:

"Answer: I know that it is a resistance that is based compositionally on the addition of added magnesium stearate and colloidal silicon dioxide."

Did I read that accurately?

A. Yes, that is exactly what I have been saying here.

MR. HAUG: Objection, Your Honor. I am not sure what counsel is doing. It looks like impeachment but it is not impeachment. He is reading from a deposition.

THE COURT: He is doing that. Mr. Miller, are you?

MR. MILLER: No, I thought I was getting a little resistance on whether he was including colloidal silicon dioxide as one of the things that imparted

resistance to water, so I wanted to clarify his answer at the deposition.

THE COURT: Well, maybe I am not, maybe I am a little thick here, but I am hearing him testify pretty consistently with what is on the page and what he is saying on the stand.

So this is your time. Go ahead and if you think you have got a space between what he is saying on the stand now and what he said there, I am prepared to let you try to explore it.

MR. MILLER: No, that was it. I am done with that portion of it. I'm going to move on.

THE COURT: Go ahead.

MR. MILLER: Thank you.

BY MR. MILLER:

Q. Thank you. Now, magnesium stearate is most commonly used as a lubricant; is that correct?

A. I would say that you're correct, that it is most commonly used as a lubricant, but this does not mean that it can't impart properties because of basic chemical picture beyond that.

Q. And magnesium stearate can be used as a lubricant before roll compaction; is that correct?

A. It can be, yes.

Q. And colloidal silicon dioxide is also used as a

glidant; is that correct?

A. Yes, that's one of the ways it's used. Yes.

Q. And it can also be used as a porization element; is that correct?

A. Yes.

Q. You testified about the dissolution testing Boston analytical performed on three of Zydus' tablets that we also heard Ms. Gray testify about this morning; is that correct?

A. Yes.

Q. In tab 2 in your binder, you'll find PTX-547R. That is the Boston analytical report; is that right?

A. It appears to be, yes.

Q. If you could go to page 7 of PTX-547R. The penultimate bullet point down there says that tablets were observed to be dissolved completely after four hours fifteen minutes.

Is that correct?

A. That's what it says, yes.

Q. And if you turn to tab three in your binder, you'll find PTX-900.1053.

A. I'm sorry. Could you say that again?

Q. Sure. Tab 3 in your binder.

A. Okay.

Q. It's that one-page document.

A. Yes.

Q. That you testified about.

And you'd recognize this as the mean dissolution profile of the Zydus tablets from the Boston analytical testing; is that correct?

A. Yes.

Q. And just to clarify again, the reason we're seeing a flat line until hour three is that hour three is when the pH 7.2 buffer was added; is that correct?

A. Yes.

Q. And as indicated by Boston analytical in PTX-547.R what you see here is that mesalamine is essentially completely released by about four-and-a-half hours in the Zydus ANDA product; is that correct?

A. Let's see. So that would be what? On this curve, seven hours and fifteen minutes, because it's four hours after the start of three I presume is the way this was written?

Q. Yes.

A. Yes.

Q. Yes.

A. Okay. Yes.

Q. Let's look at one of the pictures from this dissolution testing that you reference in your testimony. And I think we can do it from your slide deck, PDX-4.8, and that was PTX-900.93 for the record.

You testified that you know the composition of the particles floating in dissolution; is that correct?

A. What I said was that they would be the inner granules, and I told the Court what would be in the inner granules.

Q. So your testimony is that you can tell just by looking at those particles that they're composed of mesalamine, colloidal silicon dioxide and magnesium stearate; is that correct?

A. Well, what I'm saying is, is that at least most of what you see here coming out is going to be represented by what was in those pits, so that's going to be those inner granules, and you both know that what was put into them was the active ingredient, the colloidal silicon dioxide and the magnesium stearate. You know that the process that they used was a roll compaction, which is going to basically, like I described, zipper things together, is what it's designed to do. And then I guess you wouldn't expect that to change. I mean, perhaps the mesalamine is released out of there over time, so that comes out, but the rest of the stuff you would expect to be there, and that's entirely consistent with what we saw this morning with Zydus' formulator that said that would be the composition of the inner granule.

Q. But you did not do any analytical testing to

determine what the content of those particles are; is that correct?

A. No. I didn't feel like I needed to. And, in addition, I don't know exactly how I would do that.

Q. But that is a no, you did not do any analytical testing to determine the content of those particles?

A. No. I didn't feel like I needed to do that.

Q. And you testified, correct me if I'm wrong, that you know that the so-called inner volumes come from those gaps or those pits in the dissolving tablet that the red arrows are pointing to, for example; is that correct?

A. For example, yes.

Q. Now, you weren't there when these tests were performed; is that correct?

A. No, I was not.

Q. So you did not watch the tablets in realtime as they were dissolving?

A. No.

Q. And there was no video of the dissolution; is that right?

A. No. The images that were given.

Q. So there are only still photos; is that correct?

A. There are a lot of still photos, but, yes, still photos.

Q. So you cannot pinpoint precisely where any of those

particles that you are calling the inner volume come from the intact tablet there; is that correct?

A. Well, I mean, the one here that I'm pointing to on the left-hand side that looks like it's coming out of the pit.

Q. I'm sorry. You had the laser pointer. Can you do that for me?

A. Sure. It's right here (indicating). But, I mean, regardless, you have all of these pits, and you have the exact same size of what you see coming out of here, that's entirely consistent with what I would expect to see from the manufacturing process.

Q. Just to clarify, are you testifying that you can see a particular particle coming out of a particular pit?

A. Well, I'm just saying right here, it looks like a pit is forming and there's a piece here. Even if it isn't, I think, you know, all of these that are coming out that are just right near the surface are the same size of these pits.

Q. You did not do any testing to measure the size of the particles; is that correct?

A. Well, I used a ruler and I know what the size of the tablet is, right, so I can measure that. And I know then I can scale based on the ruler.

Q. You did not do that in this case, did you?

A. Yes. I think we talked about that in my deposition, how I did that.

Q. You measured the particles that are floating in the dissolution?

A. Like I said, like I told you, I used the images that you are seeing here. I used a ruler on the whole thing. If we had a big ruler, we could do it here. And then what you can do is scale it based on what you know the dimensions of the tablet are. And then you can measure what the particles are and do the same scale.

So what you get is the size scale just like we discussed in the deposition that is exactly what I would expect to see that would come through a .8-millimeter filter, which is in that first dry granulation stage, and is, in fact, exactly the same as the size of the inner granules that you saw in Dr. Davies' results earlier.

Q. So even though this is in solution --

THE COURT: Hold on just a moment.

MR. MILLER: I'm sorry.

THE COURT: Just for my own reference later. When Dr. Little said he saw a pit forming, he was pointing with his laser pointer at the red arrow on the left of PDX-4.8, which is PTX-900.93.

Go ahead.

MR. MILLER: I should have done that myself,

your Honor. Thank you very much.

BY MR. MILLER:

Q. So if you take a ruler to this, this is a product in solution; is that correct?

A. Yes.

Q. It's an image of a product in solution?

A. Yes.

Q. So if you take a ruler to it, you're assuming, are you not, that everything is in the same plane?

A. Well, I mean, I think that it most certainly can be some, a little bit more forward and some backward. I mean, a dissolution vessel is this stage. Right? So you are looking at this tablet inside of this that's this big. So you can have a little bit of back and forth.

THE COURT: All right. Again, this is all going on the record, so when you say this big, Doctor, and you put your hands together, it looks to me like you're making a cupping shape with your hand that looks to be about four inches across or something.

THE WITNESS: It's a one liter vessel. So, you know, it's about, you know, as wide as maybe my fist. And then a tablet, we all know what a large tablet -- unfortunately, we have to take big ones sometimes. They're hard to swallow. It's a relatively large tablet, 1.2 milligrams of active. So you can imagine that's in a

vessel that's about the size of my fist. If you put a tablet on the top of your fist, it's not a whole lot of before and after.

THE COURT: All right. Fine. Thank you.

MR. MILLER: You're welcome, Your Honor.

BY MR. MILLER:

Q. Now, I would like to turn to the '720 patent and talk about some of the passages that you referred to in your testimony. It's tab 1 in your binder.

A. Mm-hmm.

Q. It's DTX-1. You cited the '720 patent in column 1, lines 32 to 33. If we could go there.

A. Mm-hmm.

Q. For the proposition that inert matrices generally entail nonlinear, but exponential release of the active ingredient?

A. Yes.

Q. You did not cite in your testimony any scientific literature that supports this statement; is that correct?

A. Well, as we discussed in my deposition, these are concepts that are fairly well-known. I mean, we teach the students in the class. So these are based on -- this is based on understanding of the scientific literature.

Q. But the only publication you cite in your testimony to support the proposition that inert matrices generally

entail nonlinear, but exponential release of the active ingredient is in the '720 patent?

A. Yes.

Q. You also cited the '720 patent at column 1, lines 34 to 36 for the proposition that hydrophilic matrices have linear behavior until a certain fraction of active ingredient has been released and they significantly deviate from linear release.

Is that correct?

A. Yes.

Q. And, again, in your testimony today, you did not cite any scientific literature or references that support this statement; is that correct?

A. Yes. Again, these are concepts that are known in the field and they're known based on the scientific literature, so I didn't feel like I needed to reference that.

Q. You also cited a statement in the '720 patent at column 3, lines 57 to 59, that the claimed composition of the invention provide a release profile that is more homogeneous than traditional systems.

Correct?

A. Yes.

Q. And, again, you did not cite anything to support this statement aside from the '720 patent; is that correct?

A. Well, so this is sort of an inference, right. You

can look at the two release profiles that you would, you saw between the individual systems and you could literally, logically see how it would provide a more homogeneous release profile. So I didn't feel like I needed to cite literature for that.

Q. And because of that statement, includes the more homogeneous, it explicitly refers to a comparison with so-called traditional systems; is that correct?

A. Yes. It's in comparison to what would be observed with each of the individuals.

Q. And you performed no test in this case comparing compositions of the '720 patent to traditional systems to verify that the release profile of the patents' compositions are more homogeneous than traditional systems; correct?

A. No, I didn't need to do that, because you can see the final release profile and you don't see either one of the telltale, so you don't need to do comparison.

Q. I'd like to talk a little bit about your testimony comparing drug release profiles from Zydus' product with those of Lialda.

You testified earlier about comparison between Zydus' ANDA product and Lialda that appeared in Zydus' submissions to the FDA; is that correct?

A. No, I didn't.

Q. Did we have, I believe it was PTX-626 that was up.

I believe we're looking at ZYDUS_MES 0236592, and that's PTX-6612. And I believe you testified that these are comparing Zydus' ANDA product with Lialda; is that correct?

A. Well, what I said was in the, in the key you can see that both of them are there. The darker one is the ANDA product. The lighter one, which you can't even see at all, at least my eyes can't see at all, it says Lialda.

So if you went to the document that I referred you to afterwards that more clearly show these profiles to the Court, I listed the pH 7.2 and pH 7.5.

Q. So you have no opinion regarding similarity or dissimilarity between the dissolution profiles of Zydus' ANDA product and Lialda; is that correct?

A. Well, I didn't, I didn't bring it up on the direct, but if you were to actually look at it, and, again, it's tough to see, you could take the data out and you can look at it. I mean, they're essentially the same, but I didn't talk about it in the direct.

Q. And you have not seen any specific test results showing that Lialda embodies the claims of the '720 patent; is that correct?

A. So as we talked about this in the deposition, too. Right? I mean, Lialda is covered, it's in the Orange Book

listed as covered by the '720 patent. I understand that there were -- there's people from Zydus that were deposed that said that it's covered by the '720 patent. There are people from Shire that said it was disclosed by the '720 patent. But that's all I know.

Q. Okay. So you have not seen any specific test results showing that?

A. I have not seen specific test results, but I presume that there's something behind what Zydus' representatives and Shire's representatives testify in terms of this as being covered under the '720 patent, but I have not personally seen the data.

MR. HAUG: I was going to object. This is clearly beyond the scope of direct. Dr. Little said nothing about the '720 patent as it may relate to the Lialda product. If that's the last question.

MR. MILLER: That's the last question.

THE COURT: All right.

BY MR. MILLER:

Q. Let's look at the examples of the '720 patent. Can you turn back to DTX-1 in your binder? That's tab 1. Doctor, actually go to columns 5 and 6. That's the last example, Example 5.

Can you see the last full paragraph here? And I think this is column 6, but still describing Example 5.

It states that the dissolution profile of these tablets after a lag time of permanence in the stomach and partly in the intestine provides the release of no more than 30 percent within the first hour, no more than 50 percent within two hours, no more than 70 percent within four hours, no more than 90 percent within eight hours.

Did I read that accurately?

A. Yes. For this particular exemplified formulation, I think that you read that correctly.

Q. And Example 4 states that, tablets, the tablets described here release no more than 90 percent within eight hours.

Is that correct?

A. That's what it says, yes.

Q. Similarly, Examples 3 and 2 describe dissolutions with no more than 90 percent release within eight hours; is that correct?

A. Yes. That's what this says.

Q. And, finally, Example 1 at column 4 states that the dissolution profile of these tablets shows the release of an active ingredient in an amount lower than 90 percent at the eighth hour, thus proving that the double matrix effectively controls release.

Did I read that accurately?

A. Well, what it says is that the whole release profile

you're describing here is proven that the double matrix effectively controls the solution. So the way I would read this as someone of skill in the art even reading this whole thing is that the whole release profile is not representative of what you would see with bursting at the beginning or it goes for a certain period of time, then it would deviate. That profile is not represented by what you show there, so that's what I read.

Q. But you agree that every single example in the '720 patent describes the similar release rate where no more than 90 percent of mesalamine is released by hour eight; is that correct?

A. Well, I mean, I didn't -- I mean, I guess I would have to go through and look at each of these and see where the time points are and see what you are talking about in terms of how similar they are. I would imagine there's going to be some range because they're different formulations, but, you know, I mean, essentially what it's doing to me when I read those, it's talking the whole release profile. And the point of it, in my opinion, that it does not have that initial bursting and it does not have that dumping. And that's what I read.

Q. And turn back in your binder to tab 3, PTX-900.1053. This is a Boston analytical profile that we saw earlier. And you agreed that this shows a hundred percent release of

mesalamine in Zydus' ANDA product by about four-and-a-half hours; is that correct?

A. Yes.

MR. MILLER: I have no further questions.

THE COURT: Thank you.

Any redirect?

MR. HAUG: No redirect. Thank you.

THE COURT: Thank you, Doctor.

THE WITNESS: Thank you.

(Witness excused.)

THE COURT: Your next witness?

MR. HAUG: The next witness Shire will call will be Dr. Hoag, and my partner, Angus Chen, will examine the witness.

THE COURT: All right.

MR. CHEN: Good afternoon, Your Honor. Angus Chen, Frommer Laurence & Haug. Shire now calls Professor Stephen W. Hoag.

... STEPHEN W. HOAG, having been duly sworn as a witness, was examined and testified as follows ...

THE COURT: Thank you. Please be seated, Doctor.

MR. CHEN: May I approach, Your Honor?

THE COURT: You may, Mr. Chen.

(Mr. Chen handed a notebook to the Court.)

MR. CHEN: May I approach the witness?

THE COURT: You certainly may.

(Mr. Chen handed a notebook to the witness.)

THE COURT: I will tell you what. I will start him off with mine.

MR. CHEN: Thank you for the loan, Your Honor.

THE COURT: Thank you. Okay. We've got it worked out. Go ahead and have Mr. Gaertner have his. I've got mine. You can give it back to the court reporter after.

MR. CHEN: Okay.

THE COURT: We are on a roll.

MR. CHEN: Thank you. Thanks for the assist.

DIRECT EXAMINATION

BY MR. CHEN:

Q. Professor Hoag, could you please summarize what you were asked to do for this case?

A. Yes. I was asked to determine whether the addition of magnesium stearate and colloidal silicon dioxide to mesalamine results in some resistance to the penetration of water due to the poor affinity towards aqueous fluid.

Q. Thank you, Professor Hoag. Let's start with a little bit of your background first. What is your current position?

A. I'm a professor at the University of Maryland School of Pharmacy.

Q. What are your responsibilities as a Professor of Pharmacy?

A. At the School of Pharmacy, I teach in the pharmaceutical sciences. I do research in the area of pharmaceutical sciences. And I also do service to the school, the university, and the pharmaceutical community.

Q. And what types of classes do you teach at the University of Maryland?

A. At the University of Maryland, in the Pharm. V or undergraduate level, I teach part of a survey course in the general pharmaceutical sciences.

At the graduate level, I teach a course on the theory of solids, a course on unit operations and formulation development.

I also teach part of a course on the drug development process.

And I teach part of a course in statistics with experimental design and spectroscopy.

Q. And for how long have you been involved, approximately, in pharmaceutical formulations?

A. Including my graduate work, it's been almost 30 years or slightly over 30 years.

Q. What is the highest educational degree that you hold?

A. I hold a Ph.D. in Pharmaceutical Sciences from the University of Minnesota, Twin Cities Campus.

I also hold a Bachelor of Science in Biochemistry from the University of Wisconsin, in Madison, Wisconsin.

Q. What was the subject of your thesis?

A. My thesis involves the subject of tablet compaction.

Q. After you obtained your Ph.D., could you summarize briefly what you did?

A. After receiving my Ph.D., I did a brief stent at 3M Pharmaceuticals.

I also was a Visiting Professor at Abbott Laboratories.

My first academic position was at Oregon State University where I also had a joint appointment in the Department of Physics.

And then I joined the University of Maryland, School of Pharmacy.

Q. You mentioned earlier you do research as part of your activities. What is the focus of your research?

A. Well, my focus, my research is on solid oral dosage forms, tablets and capsules. I look at process development, formulation development, the testing, and the monitoring of processes for these products.

Q. And Professor Hoag, have you been awarded any research grants for your work?

A. Yes, I have had approximately 60 grants. As a

principal investigator, I received about almost $3 and-a-half million of grant funding. And also as a co-investigator, I received other funding. Basically, my lab has been funded continuously.

Q. Can you describe your laboratory facilities at this university?

A. At the University of Maryland, we have all the equipment needed to make tests and evaluate pharmaceutical products. We have about three 500 square foot labs.

And also, I am the director -- we have a GMP facility for which I am the director of.

Q. And I think we heard GMP earlier, but could you remind the Court?

A. It stands for good manufacturing practices.

Q. Thank you. And have you authored any publications?

A. Yes, I have had about 70 peer reviewed publications, another 20 or so non-peer reviewed publications. And with my colleague Larry Augsburger, we have written three books on tablet compaction.

Q. And do you serve on any advisory committees?

A. Yes. I have been nominated to the FDA Compounding Advisory Committee.

I am also on the USP Committee, the council of experts.

On the Handbook of Excipients Editorial Board.

And,

The Journal of Pharmaceutical Development Technology Editorial Board.

Q. Is USP the same United States Pharmacopeia that we heard of earlier today?

A. Yes, that is correct. They create the standards that the FDA in part enforces.

Q. What do you do on the USP council?

A. On the USP council, I am on the physical test methods committee, so we write test methods. We also make sure that all the test methods are current and up-to-date and evaluate those. And if people have trouble performing tests, we also help people in community troubleshoot their problems.

Q. And for how long have you been on the USP council?

A. I was first elected in 2000, and then I have been reelected a couple of times. There is a five year term for these.

Q. And do you perform any consulting work in the industry?

A. Yes. I do consulting for the pharmaceutical industry, the name brand and generic companies.

Q. And can you generally discuss or summarize your consulting activities?

A. When I do consulting, it involves formulation issues, excipients, process development, things of that nature.

Q. And besides your teaching activities at the

university, have you taught in other forums?

A. Yes, I teach a series of short courses. So they're non-degree courses that often last for about a week. So we will go to a company and teach to the company.

Also, we have done things for government agencies like the FDA, or individuals may come. We also have hands on short courses at our school. And people come in and will do a hands on course with us.

Q. And have you received any awards of note in your career?

A. Yes. I am a fellow of the American Association of Pharmaceutical Sciences.

I won the Ralph Shangraw Award for excellence in excipient research.

I also, from the USP, received an award for excellence in standard setting activities.

And then I have won some like best poster presentations at meeting awards.

Q. Professor Hoag, have you previously testified in federal court as an expert in pharmaceutical sciences?

A. Yes, I have testified in four trials previously.

Q. And did the Court accept you as an expert in any of those cases?

A. Yes, they did. In all cases.

Q. Could I please ask you to turn to PTX-572 in your

binder?

A. (Witness complies.)

Q. Do you recognize this document?

A. This is a copy of my CV.

Q. Is it current?

A. Yes. There may have been a few publications excepted only minor differences.

MR. CHEN: Your Honor, we move PTX-572 into evidence.

MR. GAERTNER: No objection, Your Honor.

THE COURT: It is admitted without objection.

(PTX-572 is admitted into evidence.)

MR. CHEN: Thank you, Your Honor.

At this point, Shire offers Professor Hoag as an expert in pharmaceutical formulation and process design and testing.

MR. GAERTNER: No objection, Your Honor.

THE COURT: All right. He is accepted as an expert. Please go ahead.

MR. CHEN: Thank you.

BY MR. CHEN:

Q. Professor Hoag, you stated earlier that you were asked to determine whether the addition of magnesium stearate and colloidal silicon dioxide to mesalamine results in some resistance to the penetration of water. Can you

summarize how you analyzed that question?

A. To address this question, we used what is called a drop penetration test.

Q. And can you provide a high level description of what a drop penetration test is?

A. The drop penetration test is where you prepare a sample. You take that sample and then you apply a known amount of water to that sample and then measure how long it takes for that water to penetrate into the sample.

Q. And is the drop penetration test used in the pharmaceutical industry?

A. Yes, it's commonly used.

Q. And do you teach the drop penetration test at all?

A. Yes. When I discussed the subject of granulation, say, my short courses or to the graduate students or the pharmaceutical students, when I teach that, I do include the drop penetration test.

Q. How many drop penetration tests have you performed yourself in your career?

A. In my career, on the order of hundreds.

Q. Okay. And how are drop penetration tests conducted?

A. The drop penetration tests that you mentioned requires a sample. So one way of performing this is that you can prepare a powder bed, prepare that at a constant. You know, you pretreat the powder, or you can prepare a

compact.

With a compact, basically what you are doing is you are taking a powder and you are squeezing that powder together until it forms a cohesive solid.

A compact is a little bit different in this context than a tablet because when we make a compact, we use the minimal amount of force to consolidate that material. And if you look at a tablet, that is done with much more force.

Q. And for your test in this case, did you use a powder bed or a compact?

A. I used the compact.

Q. Why did you choose to use a compact?

A. I choose to use the compact because I can control the variables that affect the water penetration. It's a method I have experience with. And it can also be used to minimize the differences between the control and the test specimen.

Q. Okay. And returning back to how the drop penetration tests are conducted in general. What are the different techniques for applying water in a drop penetration test?

A. To apply water to your sample, one way of doing that is to use a pipet, so you can pipet a known amount of water on the surface.

Another is to use a capillary to introduce water

to the surface.

Q. For your test in this case, which method did you choose to use to apply water?

A. I used the capillary method.

Q. Why did you use the capillary method?

A. I used the capillary method. It is a known method. It is something I have experience with, and it nicely illustrates the water penetration into the sample.

Q. Let me pause for a second and ask you, can you describe what a capillary is?

A. A capillary is a very thin tube you can use to introduce water to the sample.

Q. And how often do you use the capillary tube method in a drop penetration test?

A. I frequently use that when I am doing those types of studies.

Q. Okay. Do you teach the capillary method?

A. Yes. As I mentioned, in my short courses to the graduate students, also when I have given lectures to the FDA, I have taught this method.

Q. Okay. Now, let's look at the specific test that you conducted here in this case. What ingredients did you use in the compacts that you made?

A. I have a demonstrative prepared for that.

MR. CHEN: Can we pull up PDX-5.1, please.

BY MR. CHEN:

Q. Go ahead.

A. And so here, on the left side, in the control group, is the compact made out of 100 percent mesalamine.

On the right side, where we have our test specimen, that is comprised of mesalamine 99.3 percent, magnesium stearate 0.33 percent, and colloidal silicon dioxide, 0.41 percent.

Q. And how did you manufacture the compacts that you used?

A. If you look at the bottom of this figure here, it briefly gives an outline of how we manufacture that material.

You can see we started off with sieving the material. Oftentimes when you are doing pharmaceutical processing, you sieve the material to remove aggregates that may arise from the material. And basically the sieving, you are running it through a wire mesh to break up the aggregates.

You then blend that material in a blender.

In the case of mesalamine control, we obviously did not blend that.

Then we took a roller compactor, sometimes call it, it is called a compactor. The roller-compactor has two co-rotating wheels or rollers that compress the material together to form either a ribbon or flake.

We then take that ribbon or flake and gently mill that to produce granules.

And then, finally, we took those granules and, on a tablet press, we formed our compacts.

Q. To help us understand a little bit better visually, did you take any pictures of your experimental setup?

A. Yes, I did take a picture of the experimental setup.

Q. I am sorry. Just for one second for the record, we're looking at PDX-5.2.

And can you please describe what we see here in this picture?

A. So this is our experimental setup.

The top part of the figure there shows the mounting bracket for the capillary tube.

What we did is we mounted that tube, and we made sure that it was vertical and that it is perpendicular to the surface of the tablet. So we mounted that. Once that capillary tube was mounted, it was not moved or altered.

That black line just slightly down from the mounting bracket shows a marker of how much water we filled into it.

Below that, you can see the meniscus of the water.

And then you can see the tablet.

Now, there is a little bit of an optical illusion there. The tablet is a flat-faced tablet. So

sometimes you see tablets that are rounded, but, you know, we wanted the camera to look at the top a little bit. So that tablet is completely flat.

THE COURT: So just from my information, when you say the "meniscus," do you mean the surface level of the water?

THE WITNESS: Exactly. That curved water there. So you can tell what the height of the water is there.

THE COURT: Thank you.

BY THE WITNESS:

A. And to introduce the tablet, that is on a mounted base. As I said, we fix the capillary. Then when we wanted to have the tablet come in contact with the water, we raise the tablet up on a base. So there is what they call a lab jack that could lift that up.

Q. Professor, did you take any pictures of your experiment in progress?

A. Yes, we did. Here are some side-by-side comparisons. These are four pictures over a series of times. So you can see there is four times there.

The yellow lines indicate where the height of the water is at that specific time. And also these pictures are excerpts from the video that we took.

MR. CHEN: And just for the record, we were looking at PDX-5.3.

BY MR. CHEN:

Q. Now, Professor, you mentioned a video. Did you prepare an excerpt -- actually, did you prepare a video to show the Court?

A. Yes, this is the video that we prepared.

So basically you have the control on the left. That is pure mesalamine.

And then the magnesium stearate plus colloidal silicon dioxide and mesalamine.

Here you can see it's a sped up picture to save time. And you can see on the left how quickly the mesalamine is going down, the pure mesalamine.

And you can see now all that water is released.

Now you can see on the right side where the yellow line is, the meniscus going down.

And now you can see that the water has penetrated into the test specimen.

Q. And can you turn to the tab PTX-579 in your binder, please?

A. Yes.

Q. Is that a DVD with a copy of the video?

A. Yes. This is a DVD that is prepared with that.

MR. CHEN: Your Honor, we would like to move PTX-579 into evidence.

MR. GAERTNER: No objection, Your Honor.

THE COURT: It is admitted without objection.

(PTX-579 is admitted into evidence.)

BY MR. CHEN:

Q. Now, Professor Hoag, did you replicate your test?

A. Yes, we replicated both the control and the test specimen three times.

Q. Okay. And can you please turn to PTX-577 in your binder?

A. (Witness complies.)

Q. Do you recognize that document?

A. This is a copy of our lab notebook that we recorded the results in.

Q. Okay. And can you turn to the page, there is stamps in the middle, on the bottom, PTX-577.6.

A. (Witness complies.)

Q. What is shown on that page?

A. On this page are the summary of the drop penetration times.

So you could see there are the times that we recorded for each measurement, the three times. And below that are the average and the standard deviations.

MR. CHEN: Your Honor, we would like to move PTX-577 into evidence.

MR. GAERTNER: No objection, Your Honor.

THE COURT: It is admitted without objection.

(PTX-577 is admitted into evidence.)

BY MR. CHEN:

Q. Now, Professor Hoag, did you prepare a demonstrative to summarize your results?

A. Yes, we do have a summary demonstrative here.

Q. And is PDX-5.4 that demonstrative?

A. That is correct.

Q. Can you explain what we're looking at here?

A. Okay. These are classic bar graphs. So we have the three compacts that we tested on the X axis. So on the left side, you have the control. And the height of those bars represents how many seconds it took for that water to penetrate into the compact.

So if you look at the left, you can see that for those three compacts, we had an average time of 48.5 seconds.

We also calculated the standard deviation for these. So you could see those are 2.4 seconds.

And then we use the concept of an I beam to plot plus or minus one standard deviation. So at the top of those bars, those little I beams represent one standard deviation, so you can get an idea of the variability in those measurements.

Then on the blue, we use mesalamine, colloidal silicon dioxide, and magnesium stearate. And again, the average is 123.5.

And, again, we plotted the standard deviation, which is 13.7 in the I beam.

So this helps you kind of understand the variability and the differences relative to the variability of the measurements.

And these results show that there is a statistically significant difference between the rates of or the penetration time between the control and the test specimen.

Q. And in summary, Professor Hoag, what conclusion can you draw from your experiments?

A. So these results show that in fact the addition of magnesium stearate and colloidal silicon dioxide to mesalamine does result in resistance to the penetration of water compared to the mesalamine compact, pure mesalamine alone.

Q. I am sorry. And in your opinion, what is providing resistance to the penetration of water?

A. In my opinion, it's the magnesium stearate.

Q. And why is that?

A. Because it's such a hydrophobic material.

MR. CHEN: Thank you. No further questions.

THE COURT: All right. You may cross examine.

MR. GAERTNER: May we approach, Your Honor?

(Binders handed to the Court.)

CROSS-EXAMINATION

BY MR. GAERTNER:

Q. Good afternoon. I don't think we've had a chance to meet. My name is Mike Gaertner. I represent Zydus.

A. Good afternoon.

Q. Dr. Hoag, you described your capillary method as a known method.

MR. GAERTNER: I'm sorry about that, Your Honor.

(A binder was handed to the witness.)

THE WITNESS: Thank you.

BY MR. GAERTNER:

Q. Okay, Dr. Hoag. Sorry for that mild interruption there. I'm sure things will proceed smoothly from here on out. I want to go over your testimony a little bit today and make sure I understand things properly.

Now, you testified that your capillary method is a known method; is that right?

A. That is correct.

Q. Okay. Now, and you consider your capillary method to be a drop penetration test; is that right?

A. Yes. It's among that category of tests.

Q. All right. Now, there are hundreds of articles and references to the drop penetration test; is that correct?

A. That's correct.

Q. And you did not cite in your deposition, I'm sorry,

in your expert report an article that used the same method in this case, did you?

A. I know of methods, but I did not directly cite an article.

Q. Okay. In fact, you're not aware of a single peer-reviewed scientific reference that uses the same method that you used in this case; is that correct?

A. Actually, I am aware of methods in the literature that do use this.

Q. Okay. But in your expert report, you did not provide any references to those; is that correct?

A. In my expert report, I did not directly cite such a reference.

Q. Okay. And when you were asked at your deposition whether you're aware of any peer-reviewed articles, you were aware of none at that time; is that correct?

A. Well, at my deposition, there were several statements made. One was like, did you develop this method yourself? And I said that I had seen it in the literature, but couldn't recall at that time the exact reference.

Q. All right. And that's what I'm focusing on, Dr. Hoag, not your alleged development. It's just that at your deposition, you couldn't recall a single peer-reviewed article that used the same method that you used in this case; is that correct?

A. At the deposition, as I believe the word was something, the exact method, yes.

Q. Now, you've cited two articles in your expert report in connection with your drop penetration test, a reference by Dr. Hapgood as the lead author.

Do you remember that reference?

A. Yes.

Q. And a reference by Dr. Kayrak-Talay, who was the lead author.

Do you remember that reference?

A. Yes.

Q. Now, you consider the Hapgood reference and the Kayrak-Talay reference to be authoritative references; is that correct?

A. Yes, I do.

Q. And authoritative references on the application of the drop penetration test. I should be clear. Is that fair?

A. Yes.

Q. And one of the reasons that you believe that they're authoritative references is that they're peer-reviewed; isn't that correct?

A. That is correct.

Q. Now, aside from your expert report in this case, you have not delivered an expert report in which you used the

same method as you've done in this case; is that correct?

A. Could you repeat that question?

Q. Sure. Aside from your expert report in this case, you have not prepared an expert report in any other case in which you have used the same method as you've done in this case; is that correct?

A. That's correct.

Q. And you have not published any articles in any peer-reviewed references describing the capillary method that you use in this case; is that correct?

A. I have done studies, but they have not led to the publication of peer-reviewed articles.

Q. So you have no study results that have been published in peer-reviewed articles using this capillary method; is that correct?

A. That's correct.

Q. Now, I'm trying to make sure I get a handle around what it is that you are offering an opinion on.

In your expert report, you stated that you endeavored to simulate the inner volume of the granules of the Zydus ANDA product.

Is that what you endeavored to do?

MR. CHEN: Your Honor, objection. Outside the scope of direct. Professor Hoag did not mention anything on the --

MR. GAERTNER: Your Honor --

THE COURT: Let me hear the question again.

MR. GAERTNER: I'm confused about the opinion that he offered because it differs from the one in his expert report.

THE COURT: So --

MR. GAERTNER: Okay.

THE COURT: Let me hear the question again.

MR. GAERTNER: Sure.

THE COURT: Let me have it again.

MR. GAERTNER: In his expert report, he stated that he endeavored to simulate the inner volume of the granules of the Zydus ANDA product.

THE COURT: That's the question? Okay. Well, overruled. Until I hear where this is going, I don't know whether it's within the scope or not.

Go ahead. Thank you.

MR. CHEN: Thank you, Your Honor.

BY MR. GAERTNER:

Q. Is that correct?

A. Does that mean I answer the question?

THE COURT: That means you answer the question.

THE WITNESS: Okay. Could you repeat the question?

BY MR. GAERTNER:

Q. Sure. You remember submitting an expert report in this case; is that correct?
A. Yes.
Q. All right. Now, in your expert report, you stated that you endeavored to simulate the inner volume of the granules of Zydus' ANDA product; is that correct?
A. That terminology, or, yes, that is in the expert report.
Q. Now, are you offering an opinion on the alleged lipophilicity of the inner volumes of the Zydus ANDA product?
A. Really, what I'm offering an opinion on is the test that I've described in my testimony.
Q. All right. And I'm trying to understand, are you testifying as to the lipophilicity of the alleged granules in the Zydus product or the tablets that you put together and ran your drop penetration test on?
A. My opinion is related to the study that I described and those tablets that I showed in the video.
Q. Okay. So the study that you described was on the tablets that you made, not on the granules that are alleged to be in the Zydus ANDA product; is that correct?
A. Well, I mean, as you recall in my expert report, there was some statement about that they are the -- that was a basis of what I designed those granules, but I'm not

offering an opinion about whether they, you know -- I'm just offering an opinion about that test there.

Q. Yes. Well, I'm trying to bring that to this case, Dr. Hoag, and make sure that I ask you questions that are within the scope and that make sense for the Judge.

Are you offering an opinion today about the alleged lipophilicity of what is called the granules in the Zydus ANDA product?

A. No.

Q. Dr. Hoag, you also have been hired as an expert by the plaintiffs in another Lialda generic case against Mylan; is that correct?

A. I didn't hear the first part of that.

Q. Sure. You're also serving as an expert for the plaintiffs in this case and another case they have against Mylan; is that correct?

A. That is correct.

Q. All right. And you prepared an expert report in that case; is that correct?

A. That is correct.

Q. In which you tested the Mylan product for alleged lipophilicity; is that correct?

A. That was in that report, yes.

Q. Okay. And in the Mylan expert report, you used a different test than you used against the Zydus product; is

that correct?

A. That's correct.

Q. Now, with respect to the drop penetration time, Dr. Hoag, I'm trying to get a sense for when in that time you can decide the difference means that a tablet like you tested is lipophilic.

Now, there was a period of time, I think it was, and I will get my notes here -- you've got it on your PDX-5.4 and there's a time difference there. That on average, what you call your control compacts for 48.5 seconds and your test at an average of 123.5. Okay?

You can look at it on your own chart --

A. Yes.

Q. -- on PDX-5.4.

Now, you talked about the difference in time water absorption into the compacts that you made. At what point in time can you determine whether or not you consider in this example the compact on the right, which is in the blue bars, is lipophilic?

A. When there's a significant difference between the test and the compact.

Q. Okay. And in this example, the blue bars are the compacts you made. Two-and-a-half times longer would be absorbed in the contacts than the large bar compacts; is that right?

A. Approximately, yes.
Q. And is that what you would characterize as a significant difference?
A. Well, statistically significant is based on statistical principles. The difference you see between two measurements is unlikely to be the result of chance, so that there's enough difference that you are fairly certain that there's a real difference between those samples.
Q. Now, in your expert report you did not point to any scientific references which would give a person of ordinary skill in the art a basis to determine whether or not a specific time difference in water penetration time, even if your capillary method is accepted, would result in a finding of lipophilicity; is that correct?
A. Could you repeat that question, please?
Q. Sure. It was a mouthful and I apologize for that.

I want to go back to your expert report. In your expert report, you do not cite to any scientific references in which a person of ordinary skill could look to determine when in a point of time something would be judged lipophilic in your capillary test; is that correct?
A. Yes. The test is a relative scale, so you have a control, and then you have your test specimen, and when there's a statistically significant difference, then you can draw conclusions about the rate of water penetration.

Q. All right.
A. And the resistance to water penetration.
Q. Sure. And my point, in your expert report, you did not cite to any scientific references which applied that standard or test; is that correct?
A. Well, I mean, there's 500 million statistic books out there. If there's a real difference between materials, I don't feel like this is such a common knowledge that was required to be submitted.
Q. Sir, I'm just asking you a really small question. In your expert report, did you cite to any scientific references that applied that sort of a test?
A. The test being a "T" test?
Q. The test that you applied here to measure lipophilicity in your opinion?
A. Well, the Hapgood article.
Q. Now, the Hapgood article is a drop penetration test; is that correct?
A. Right.
Q. All right. You did not perform a drop penetration test as is described in the Hapgood article; is that correct?
A. I used the capillary version of the drop penetration test.
Q. Well, the Hapgood reference does not describe a

capillary method, does it?

A. No, it does not.

MR. GAERTNER: One moment.

(Pause while counsel conferred.)

MR. GAERTNER: I have nothing further, Your Honor.

THE COURT: All right. Thank you.

Any redirect, Mr. Chen?

MR. CHEN: No, Your Honor. Thank you.

THE COURT: Thank you, Dr. Hoag.

THE WITNESS: Thank you. Do I just leave this here?

THE COURT: Why don't you just take that, Mr. Chen? Thanks so much.

(Witness excused.)

THE COURT: Mr. Haug?

MR. LIEF: Our next witness will be Dr. Scott Hanton. He performed some tests that go to melting point issues.

THE COURT: All right. Thank you.

... SCOTT HANTON, having been duly sworn as a witness, was examined and testified as follows ...

MR. LIEF: If we might approach with the books?

THE COURT: You may. Both the bench and the witness.

(Notebooks handed to the Court and to the witness.)

THE COURT: Please proceed.

DIRECT EXAMINATION

BY MR. LIEF:

Q. Dr. Hanton, good afternoon. Can you tell us, what's your profession?

A. I'm an analytical chemist and business manager.

Q. And can you briefly describe your educational background?

A. I earned a Ph.D. in physical chemistry from the University of Wisconsin at Madison and a Bachelor's degree in chemistry from the Honors College at Michigan State University.

Q. And could you briefly describe your career after you earned your Ph.D.?

A. Once I finished my education, I went to work at Air Products and Chemicals, in their global analytical sciences department. I served there in a variety of capacities, from research bench chemist to technical manager.

As the technical manager, I was responsible for a variety of laboratories, including chromatography, including GL and LC spectroscopy, which included FTIR and NMR, thermal analysis, which included DSC and TGA, and mass spectrometry.

That business was outsourced by Air

Products to Intertek in 2010. I've been at Intertek since, where I'm now the general manager and the chief scientist.

Q. And there were a few acronyms in there. If I could get them explained on the record. You said GC?

A. GC is gas chromatography.

Q. And any others?

A. DSC is differential scanning calorimetry. TGA is thermogravimetric analysis. FTIR, Fourier transform infrared analysis.

Q. All right. After Air Products, you said you went to Intertek. Can you describe your role at Intertek?

A. Yes. I am responsible for the entire business of the research labs at Intertek in Allentown, Pennsylvania. There I work closely with integrated teams of analytical chemists, where we do primarily problem solving, new methods development, analysis, and testing on chemicals and materials.

Q. All right. Apart from your industry experience, have you published any scientific articles?

A. Yes. I've done independent research and I have published about 35 peer-reviewed papers and book chapters.

Q. If we could turn in your book to PTX-549, and could you tell us what this document is?

A. Yes. This is my C.V.

Q. And is the information contained in this C.V.

accurate and up to date?

A. Yes, it is, save for a few minor additions of a presentation or paper and a slight change in title.

Q. All right.

MR. LIEF: We would move PTX-549 into evidence.

MR. GAERTNER: No objection.

THE COURT: Admitted without objection.

(PTX-549 was admitted into evidence.)

MR. LIEF: And we would offer Dr. Hanton as an expert in chemical analysis and analytical techniques.

MR. GAERTNER: No objection.

THE COURT: All right. The doctor is admitted as an expert. Please proceed.

BY MR. LIEF:

Q. Dr. Hanton, what have you been asked to do in this case?

A. I've been asked to conduct property and thermal property analysis on magnesium stearate that's from the Zydus ANDA product.

Q. If we could take a look at PDX-6.1. Can you tell me what this is?

A. This is a summary of the analyses that we did on the samples. Infrared analysis is using absorption of infrared light to get a fingerprint of a chemical substance to identify chemical substances.

TGA is where we take a small amount of a material, put it into a furnace where it has a constant temperature ramp and measure the weight of it during that ramp. We're looking to see if any portion of the substance might leave with high temperature.

Gas chromatography with mass spectrometry is a technique that's commonly used to separate complex mixtures and identify the substances therein.

Gas chromatography with flame ionization is very similar. It's a technique to separate complex mixtures and quantify the substances there in.

Differential scanning calorimetry is measuring the transfer of heat into a material to find out whether it absorbs or emits heat. It's comparing a sample to an empty pan.

Q. All right. Are these techniques routine analytical techniques?

A. Yes. These are routine tests that are commonly used both at Intertek and in the field. They are very reliable to measure chemical composition and thermal properties.

Q. And who developed the specific procedures that were used at Intertek for these tests for this case?

A. I developed the procedures that we used for these samples. I worked closely with the scientists who did the work. I supervised them, and then I reviewed and signed off

on the work as it was conducted.

Q. If we could turn to PDX-6.2. Can you tell us what is shown here?

A. Here, we see individual pages from the notebooks where the work was documented. On each of these pages we see that the sample, magnesium stearate that was analyzed has an identification number of ZYDUS_MES 0346399, and that relates back to a batch number of 0908123024.

Q. All right. I would like you to turn in your book to several PTX's, PTX-559, 560, and 561.

And if you could identify what those three documents are.

A. Yes. These are the laboratory notebooks that were used for the analysis of these samples where the procedures and results were documented.

Q. All right. Is it Intertek's regular practice to use lab notebooks for document testing?

A. Yes, it is.

Q. And were these lab notebooks maintained in the ordinary course of Intertek's business?

A. Yes, they were.

MR. LIEF: We would move PTX-559, 560, and 561 into evidence.

MR. GAERTNER: No objection.

THE COURT: Admitted without objection.

(PTX-559, 560 and 561 were admitted into evidence.)

BY MR. LIEF:

Q. I'd like to turn to PTX-558. And can you tell us what this is?

A. Yes. This is the results of the infrared analysis that we conducted. On the Y axis going up and down, you can see the absorbance, which is telling us how much of a particular stretch or band is present in the sample.

On the X axis, we're seeing the wave numbers, which corresponds to the color frequency of the light that was used. In this particular figure, we're comparing two different infrared traces. The blue one comes from the magnesium stearate from the ZYDUS_MES product, and the red one comes from a magnesium stearate from the USP standard. They're very similar, essentially identical, except for a little difference around 3259 wave number.

Q. And what is the significance of the 3259 wave number?

A. That is the area of the IR spectrum where a hydrate would absorb. So this is showing us that both samples are hydrated and that the Zydus magnesium stearate is a bit more hydrated than the USP standard.

MR. LIEF: We would offer PTX-558 into evidence.

MR. ABRAMOWITZ: No objection.

THE COURT: It's admitted.

(PTX-558 is admitted into evidence.)

BY MR. LIEF:

Q. You mentioned you conducted a thermogravimetric analysis or a TGA. Can you briefly describe in a little bit more detail what that means?

A. Yes. In a TGA experiment, we'll take a small amount of the sample, place it into a pan and put it on a very precise balance to weigh how much material is present. We then put that into a furnace and expose the sample to a constant temperature ramp to relatively high temperatures.

The object is to find out if any material is leaving the sample due to that high temperature exposure.

MR. LIEF: All right. If we could turn to PTX-552.

BY MR. LIEF:

Q. Can you tell us what this is?

A. This is the result of our TGA experiment.

On the left axis going up and down is the percentage of weight of the sample. At the top, we see 100 percent where we started. The bottom, please note is at 96 percent. So we're only showing the weight loss region of interest.

The X axis is the temperature, so that is the temperature that the furnace went to, that was exposed to the sample during the course of the experiment.

And during this TGA experiment, we see weight

loss as shown by the green curve. And the total weight loss for this experiment was about 3.7 weight percent.

MR. LIEF: Again, we would offer PTX-552 into evidence.

MR. ABRAMOWITZ: No objection.

THE COURT: It is admitted without objection.

(PTX-552 is admitted into evidence.)

BY MR. LIEF:

Q. I'd now like to pull up PTX-554. And can you tell us what this is showing?

A. This is a result of the GC/MS experiment.

On the Y axis, going up and down, is the intensity of the ions that we observed during the experiment.

On the X axis is the time by which they were separated in the instrument.

We see a variety of species within the magnesium stearate sample, the most important of which are magnesium stearate and magnesium palmitate.

Q. And again you had mentioned an acronym there "GC/MS." Can you tell us what that stands for?

A. GC/MS stands for gas chromatography with mass spectrometry.

MR. LIEF: We would offer PTX-554 into evidence.

MR. ABRAMOWITZ: No objection.

THE COURT: It is admitted without objection.

(PTX-554 is admitted into evidence.)

MR. LIEF: Turning to PTX-557.

BY MR. LIEF:

Q. Can you tell me what this is?

A. This is the result of the GC flame ionization experiment.

Again, on the Y axis is the intensity of species we see at the detector.

The X axis is the time of solution coming out of the GC experiment.

We see very similar results that we saw in the GC/MS experiment.

We see the same series of species observed within the sample. Again, the most important and the highest peaks are the magnesium stearate and magnesium palmitate.

THE COURT: Tell me what you mean when you say "species" in this context.

THE WITNESS: In this context, they're different individual chemicals that are part of the sample.

THE COURT: All right. Thank you.

MR. LIEF: So we would move PTX-557 into evidence.

MR. ABRAMOWITZ: No objection, Your Honor.

THE COURT: It is admitted without objection.

(PTX-557 is admitted into evidence.)

BY MR. LIEF:

Q. I'd like to turn to what, as an acronym, we have been calling DSC or differential scanning calorimetry. Can you explain a little bit more what that is?

A. Yes. In a differential scanning calorimetry experiment, we take a small amount of the sample in question and put it into one pan. And then in another pan, we leave empty. Both of those pans are inside of a furnace.

So we're going to now raise the temperature in a linear rate and measure the heat flow that is going through the pans. Of course, being in a furnace, they're going to get hot, but we are measuring the relative differential of the heat flow from the sample into the empty pan. And at any given temperature during the DSC experiment, the sample might absorb heat, we see that in the negative, or give off heat, we would see that in the positive. And the instrument is then adding those together, and we see the net heat change at any given temperature.

Q. If we turn to PTX-553, can you tell us what this is?

A. Yes. This is the result of the DSC experiment that we did on the magnesium stearate sample.

On the Y axis, going up and down, is that heat flow that I measured, I described.

On the X axis is the temperature rate of what

the temperature is going through in the oven.

The green curve is showing the heat flow, the differential heat flow through the sample as compared to the empty pan. And at any given point, it is measuring the net of heat released from the sample or heat absorbed by the sample.

And in this particular experiment, we see two key endotherms.

Q. And when you say "endotherm," what do you mean by that word?

A. And endotherm is demonstrating where the sample is absorbing heat compared to the empty pan.

Q. All right. And I also see on there some numbers for that first endotherm on the left. What is the number up top there?

A. We see for each of the two key endotherms, we're measuring onset temperature. That onset is measured by taking the steepest point of the slope where we see the endotherm and extending it backwards to the drawn baseline across the top of the endotherm.

Where that steepest slope intersects with the baseline is the onset temperature.

For the first endotherm, that onset temperature is 82.9 degrees C, and for the second endotherm, that onset temperature is 126.2 degrees C.

Q. Is the way you describe determining the onset temperature for the endotherm, is that a standard technique for determining onset?

A. Yes, it is.

MR. LIEF: We would offer PTX-553 into evidence.

MR. ABRAMOWITZ: No objection.

THE COURT: That's fine. And it's admitted without objection.

(PTX-553 is admitted into evidence.)

THE COURT: And you can certainly object to my questioning, if you want, but I have a question about that. So can you, Mr. Lief.

What is the scientific principle or reason, if you can answer without speculating, why you would have two endotherms? What is going on?

THE WITNESS: There is some change in the chemistry, and so there is multiple effects that can occur where chemistry may -- in this case, their endotherms may absorb heat, so there can be two or more different processes where heat is absorbed.

MR. LIEF: And just as a --

THE COURT: With the same compound?

THE WITNESS: The compound may be changing during the course of this experiment.

THE COURT: Because of the heat.

THE WITNESS: Because of the heat.

THE COURT: All right. Thank you.

MR. LIEF: Just as a foreshadowing, I believe our next expert, probably tomorrow morning, Dr. Pinal, will address those questions very specifically based upon this.

THE COURT: All right. Thank you.

MR. LIEF: Did I move 553 into evidence?

THE COURT: I believe you did, and it was admitted without objection.

MR. LIEF: All right.

BY MR. LIEF:

Q. If we could turn to Plaintiffs' Demonstrative Exhibit 6.3. Can you tell us what is shown here?

A. Here are the key conclusions from the analytical testing I conducted on the magnesium stearate.

First of all, the infrared analysis confirms that the sample I tested is indeed magnesium stearate and it show that it is in its hydrated form.

The TGA analysis shows a 3.7 percent weight loss. It is consistent with a hydrated magnesium stearate that lost the water of hydration.

The GC analysis showed that the sample contains 65.4 percent magnesium stearate, and 33.4 percent magnesium palmitate, and small amounts of other fatty acid substances.

The DSC analysis shows two key endotherms, the

first having an onset at 82.9 degrees C and the second have having an onset of 126.2 degrees C.

MR. LIEF: Thank you. No further questions.

THE COURT: All right. Thanks.

Cross-examination.

MR. ABRAMOWITZ: We have no cross-examination.

THE COURT: All right. Thank you, Doctor. You may step down.

THE WITNESS: Thank you.

THE COURT: Mr. Haug.

MR. HAUG: We have run out of witnesses.

THE COURT: Okay.

MR. HAUG: We do have a deposition but I don't know that we want to --

THE COURT: Well, I'm happy to, if you have a depo and you can use our last 15 minutes or so here.

(Counsel confer.)

MR. HAUG: Actually, Your Honor, I am told we're not because it was a deposition we don't have to put in because of our agreement.

THE COURT: All right. Then let me ask you some logistical questions; all right?

How are we doing in terms of moving the case along? Are we about on track? Are we ahead of schedule? Where are we?

MR. HAUG: For us, Your Honor, we're very much on schedule. As you know, we have had seven or eight witnesses today. So we were hoping to get through all our list, and we did. So I think we're on schedule. I suspect we will probably finish our case, subject to cross-examination, obviously, sometime tomorrow for sure. How long of a day, I don't know.

THE COURT: All right.

MR. GAERTNER: Yes, I just wondered. Obviously I want to make sure of everybody's thought and view if Mr. Haug has an idea. In the afternoon?

MR. HAUG: Well, I think we have three, two or three more witnesses, so I would say sometime early afternoon maybe, again, subject to cross. They're key experts so I don't know how long they will be.

THE COURT: Sure. But the important thing is we want to have Mr. Gaertner's folks teed up and ready to start.

I imagine we'll have some argument or motion practice perhaps, but we ought to have something ready to go in the afternoon, it sounds like, from the defense side. Okay?

MR. HAUG: And they have already identified people they say are ready to go as soon as we finish tomorrow.

THE COURT: All right. Let me encourage both

sides, if you would, to take a moment then this afternoon to visit with the courtroom deputies to make sure that everything you thought was in evidence is actually marked on the record as in evidence and that the time is consistent, reasonably so, with what you expect the time allocation to be.

And with that, we'll go ahead and recess. I'll see you all tomorrow at 9:00 a.m.

(Proceedings adjourned at 4:19 p.m.)

I hereby certify the foregoing is a true and accurate transcript from my stenographic notes in the proceeding.

/s/ Brian P. Gaffigan
Official Court Reporter
U.S. District Court